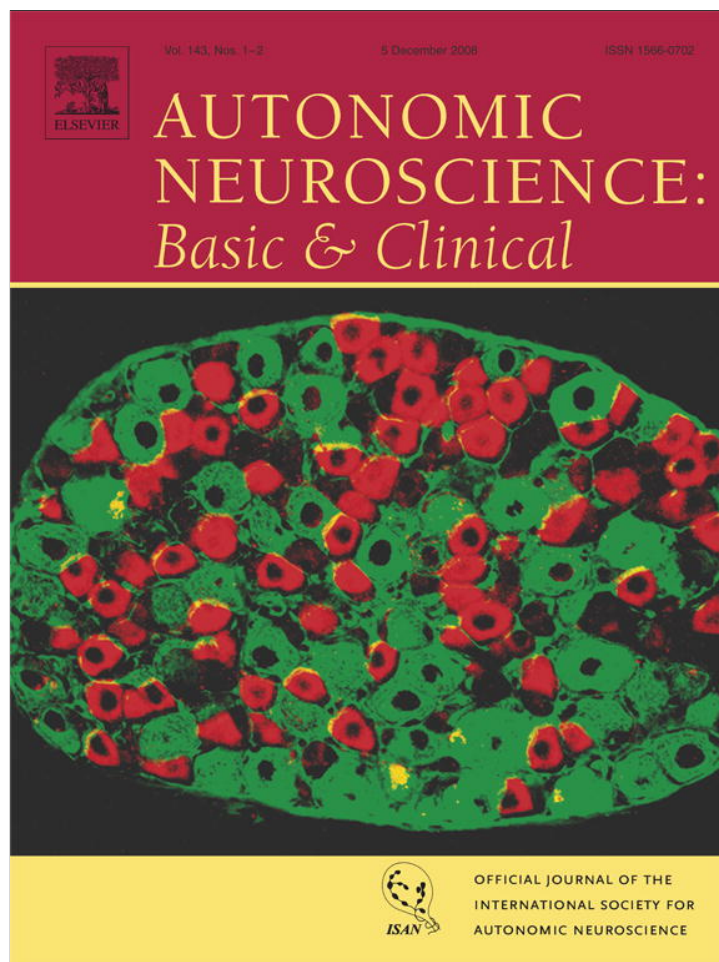


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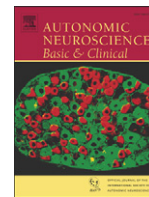
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Effects of strenuous exercise on autonomic nervous system activity in sickle cell trait carriers

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ABSTRACT

This study compared the nocturnal autonomic nervous system (ANS) activity in seven sickle cell trait (SCT) carriers and six subjects with normal hemoglobin in response to exercise. Sympathetic and parasympathetic indices of nocturnal ANS were measured in the two groups before and 24 and 48 h after a strenuous exercise consisting of the repetition of three maximal exercise bouts. Global ANS activity decreased 24 h after exercise in both groups and was lower before as well as after exercise in SCT carriers. Indices of parasympathetic activity were lower in SCT carriers at all times, indicating a persistent sympatho-vagal imbalance. Exercise did not cause a rebound in parasympathetic activity in either group, but a rebound was noted for sympathetic index values two days after exercise in SCT group only. The ANS activity was generally lower, and the sympatho-vagal imbalance greater, in SCT carriers compared with control subjects irrespective of exercise and could increase the risk for medical complications in this population.

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1. Introduction

A decrease in autonomic nervous system (ANS) activity is a recognized predictor of severe cardiac and cerebral events, cancer and death of any cause in the general population (ESC/NASPE-Task-Force, 1996; Kleiger et al., 2005; Tsuji et al., 1996). ANS activity and sympatho-vagal balance is most often measured through heart rate variability (HRV) indices. These indices are mostly used to predict post-myocardial infarction outcome (Bigger et al., 1992; La Rovere et al., 1998), but they are also useful to evaluate specific risks in other populations such as diabetic patients (Freeman et al., 1991) and subjects with anemia, including vitamin B₁₂ deficiency and thalassemia major (Franzoni et al., 2004; Sozen et al., 1998).

Sickle cell trait (SCT), although previously considered as a benign disorder (Ashcroft and Desai, 1976; Hoiberg et al., 1981), seems to signal the presence of risk factors for cardiovascular complications. These factors include altered sympatho-vagal balance (i.e. low parasympathetic activity and high sympathetic activity), high blood viscosity, decreased red blood cell deformability and elevated concentrations of soluble adhesion molecules at rest (Connes et al., 2005, 2006b; Monchanin et al., 2005; Reid and Obi, 1982). Higher predispositions for developing coronary artery disease (Ould Amar

et al., 1999) and venous thromboembolism (Austin et al., 2007) have been reported in the SCT population than in control subjects.

Whether the abnormalities associated with SCT contribute to the exercise-related sudden deaths reported in this population has been a recent subject of debate (Connes et al., 2007; Dincer and Raza, 2005; Jones et al., 1970; Kark and Ward, 1994; Le Gallais et al., 2007). In this regard, ANS activity may be a strong link between exercise and sudden death (Curtis and O'Keefe, 2002). Whereas long-term training was shown to provide a high degree of protection against sudden cardiac death through the gain in parasympathetic activity (Hull et al., 1994), the transient immediate response of ANS activity to exercise is a decreased parasympathetic activity (Furlan et al., 1993; Hautala et al., 2001; Hayashi et al., 1992). No study, however, has yet investigated ANS activity in SCT carriers in response to an exercise session.

Hence, we designed a prospective longitudinal study to compare measurements of ANS activity in SCT carriers and non-carriers before and following intense exercise. We hypothesized that strenuous exercise would induce greater alterations in the sympatho-vagal balance in SCT carriers than that observed in non-carriers.

2. Materials and methods

2.1. Subjects

Thirteen male Afro-Caribbean subjects participated in this study: seven SCT carriers (SCT group, 21.1 ± 1.1 yrs, 177.9 ± 2.4 cm, 72.8 ± 5.1 kg) and six subjects with normal hemoglobin (control group, 19.5 ± 0.5 yrs,

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179.7±2.3 cm, 75.4±2.0 kg). The hematological characteristics of the subjects are summarized in Table 1. All were students at the University of French West Indies and Guyana. Exclusion criteria included apparent metabolic, muscle, heart, or pulmonary diseases, malaria, anemia and/or alpha-thalassemia. The subjects were all volunteers and provided informed written consent. The protocol was approved by the local Ethics Committee.

2.2. SCT detection and hematological parameters

To test for the hemoglobin type, venous blood was drawn at rest into tubes containing EDTA and screened by isoelectric focusing. The results were confirmed by citrate agar electrophoresis. The various hemoglobins were isolated and quantified by high performance liquid chromatography (HPLC). A test of solubility confirmed the presence of Hb S. Positive test results for SCT were determined by the presence of Hb S (<50%) and a normal percentage of Hb A2. Hemoglobin concentration (Hb), hematocrit (Hct), percentage of reticulocytes (Ret) and mean corpuscular volume (MCV) were determined with a hematology analyzer (Max M-Retic, Coulter, USA) and were used for the indirect diagnosis of anemia and alpha-thalassemia, which results in hematological modifications (Embury, 1988).

2.3. Exercise protocol

All the subjects performed an exhaustive exercise on cycle ergometer (Ergoline, Bitz, Germany) between 8 and 11 a.m. Pedalling speed remained constant (at 70 rpm) throughout testing. The trial consisted of the repetition of three progressive and maximal ramp exercise tests interspaced with 10 min of recovery (5 min of easy pedalling and 5 min of rest) to mimic an exercise situation often encountered by sportsmen in their training session. The first test began with a 3-min warm-up at 60 W and the load was increased by 30 W every minute until maximal oxygen consumption (VO_{2max}) was reached. The two following exercise repetitions began directly with a 1-minute step at 60 W and the load was also increased by 30 W every minute until maximum exercise capacity was reached. Oxygen uptake measured during the first exercise test (breath-by-breath automated exercise metabolic system Vmax29, SensorMedics, Yorba Linda, CA, USA) was considered maximal if at least three of the following criteria were met: 1) a respiratory exchange ratio greater than 1.10, 2) attainment of age-predicted maximal heart rate (HR_{max}) [$210 - (0.65 * age)$], 3) an increase in oxygen uptake (VO_2) lower than 100 ml with the last increase in workload, and 4) an inability to maintain the required pedalling frequency (70 rpm) despite maximal effort and verbal encouragement. The maximal aerobic power (MAP) output and the global exercise test duration (ETD, i.e., without the recovery times) were calculated.

To measure ANS activity, an electrocardiogram was recorded using an ambulatory 24-hour electrocardiogram Holter device (Novacor system, Duosoft, Rueil-Malmaison, France) the night before the test (corresponding to TR) as well as the two nights following the exercise (i.e., T24H and T48H).

Table 1

Maximal exercise responses determined during the first test in the two groups

| | Control group | SCT group |
|-------------------------|---------------|-----------|
| VO_{2max} (ml/kg/min) | 34.9±1.7 | 33.4±1.1 |
| MAP (W) | 285±7 | 274±12 |
| HR_{max} (beats/min) | 186±2 | 182±2 |
| ETD (min) | 25±1 | 25±1 |

Values are mean±SEM. VO_{2max} (maximal oxygen uptake), MAP (maximal aerobic power), HR_{max} (maximal heart rate), ETD (exercise duration time; i.e., total duration of pedaling throughout the three exercise tests). No significant difference between the two groups.

Table 2

Hematological parameters in the two groups

| | Control group | SCT group |
|-------------|---------------|-----------|
| [Hb] (g/dl) | 15.1±0.2 | 15.1±0.2 |
| Hct (%) | 45.6±0.6 | 44.0±0.5 |
| Ret (%) | 0.7±0.1 | 0.9±0.1 |
| MCV (fl) | 88.0±1.0 | 84.0±1.0 |
| HbS (%) | – | 38.4±0.9 |

Values are mean±SEM. [Hb] (hemoglobin), Hct (hematocrit), Ret (percentage of reticulocytes), MCV (mean corpuscular volume), Hb S (hemoglobin S). No significant difference between the two groups except for Hb S.

All the subjects were asked to avoid physical exercise for at least 3 days before the test and no drink was allowed 3 h before and during exercise.

2.4. ECG data analysis

The electrocardiographic Holter system (Novacor system, Duosoft, Rueil-Malmaison, France) allowed us to extract the RR intervals list with a precision of 0.008 s. Each RR interval was validated before analysis. We chose to analyze only the night periods to avoid introducing variations due to differences in physical activity or environment (Fortrat et al., 1999). The beginning and end of the sleep periods were read from the activity questionnaires and verified from the 24-hour RR intervals plots.

2.5. Mean heart rate and time domain analysis

On each recording, we calculated the mean heart rate (beats per minute, bpm) and the following indices of heart rate variability over a continuous 4-hour period: the proportion of adjacent normal RR intervals differing more than 50 ms from the preceding RR (PNN50), the standard deviation of all normal RR intervals (SDNN), the square root of the mean of the sum of the squared differences between adjacent normal RR intervals (RMSSD), the standard deviation of the mean of all normal RR intervals for 5-minute segments (SDANN), and the mean of the standard deviation of all normal RR intervals for all 5-minute segments (SDNNIDX).

2.6. Fourier analysis

The fast Fourier transform indices were calculated on sets of 256 consecutive RR intervals during the night periods. The power spectrum indices were calculated as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (ESC/NASPE-Task-Force, 1996). The high frequency peak of the spectrum (HF, 0.15 to 0.40 Hz) is known to represent parasympathetic activity, and the low frequency (0.04 to 0.15 Hz) represents both parasympathetic and sympathetic activities. Additional calculations included: the very low frequency power (0 to 0.04 Hz), the LF/HF ratio, the normalized low and high frequency power (LF nu and HF nu) as $100 * LF / (total\ power - VLF)$ and $100 * HF / (total\ power - VLF)$, respectively, and the total frequency power (Ptot).

2.7. The meaning of the ANS activity parameters

Although recently debated (Parati et al., 2006; Taylor and Studinger, 2006), it is usually admitted that some variables are mainly under the control of parasympathetic activity (PNN50, RMSSD, HF, HFnu), sympathetic activity (SDNNIDX, SDANN), or global autonomic activity (SDNN, Ptot) (ESC/NASPE-Task-Force, 1996). The very low frequency of spectrum (VLF) contains partially parasympathetic activity and is predictive of clinical prognosis in cardiac patients (Hadase et al., 2004), the low frequency indices (LF and LFnu) contain

Table 3

Raw values of time domain analysis in the nocturnal period for both groups before exercise (rest) and 24 and 48 h after exercise (T24H and T48H, respectively)

| | Control group | | | SCT group | | |
|------------------|---------------|-------------------------|------------|-------------|------------------------|-----------|
| | Rest | T24H | T48H | Rest | T24H | T48H |
| RR interval (ms) | 1146±32 | 1080±23 | 1133±28 | 987±56* | 981±42* | 965±26* |
| PNN50 (%) | 28.5±2.7 | 28.3±3.1 | 29.5±2.5 | 19.9±3.5* | 20.2±3.1* | 19.8±1.2* |
| SDNN (ms) | 155.0±11.0 | 128.5±13.0 [†] | 137.8±11.1 | 125.1±11.3* | 109.9±7.4 [†] | 125.2±4.5 |
| RMSSD (ms) | 113.7±14.1 | 101.6±11.6 | 112.0±13.6 | 70.2±10.0* | 68.3±7.3* | 67.8±4.0* |
| SDANN (ms) | 75.5±6.0 | 59.7±9.2 | 55.0±3.7 | 65.3±6.7 | 51.7±7.3 | 71.5±5.7 |
| SDNNIDX (ms) | 123.7±11.9 | 107.9±9.8 | 118.9±11.1 | 97.0±9.9 | 88.5±6.4 | 94.3±4.7 |

Values are means±SEM. *Significant difference between groups $P<0.05$; [†] significantly different from rest $P<0.05$. SDNNIDX tended to be lower in SCT carriers than in the control group (group effect; $P=0.06$) and tended to be decreased by exercise in both groups (time effect; $P=0.08$).

both sympathetic and parasympathetic activities, and the LF/HF ratio has been proposed as a marker for autonomic nervous system balance (ESC/NASPE-Task-Force, 1996).

2.8. Statistical analysis

The results are expressed as mean±SEM. The hematological parameters, the maximal exercise responses obtained during the first repetition of exercise (VO_{2max} , MAP and HR_{max}), and the exercise test duration (ETD) were compared between the two groups using an unpaired Student *t* test. The HRV data were compared between the two groups using a two-way ANOVA for repeated measures. Pair-wise contrasts were used when necessary to determine where significant differences had occurred. Statistical analyses were performed with Statistica (v5.5, Statsoft, USA). The significance level was defined as $P<0.05$.

3. Results

3.1. Hematological parameters and exercise responses

As shown in Tables 1 and 2, neither the exercise (VO_{2max} , MAP, HR_{max} and ETD) nor the hematological ([Hb], Hct, Ret and MCV) parameters differed between the groups.

3.2. ANS activity data

The time domain and spectral parameters are shown in Tables 3 and 4, respectively.

3.2.1. Group effect

When the three consecutive measurements were taken together (i.e., TR, T24H and T48H), we observed a marked significant group effect between SCT carriers and non-carriers for the following parameters: RR intervals, PNN50, RMSSD, SDNNIDX, Ptot, HF, and HFnu, all of which were lower in SCT carriers, and LFnu and LF/HF, which were higher in this group. SDNN was lower in SCT carriers than in controls at TR but not at T24H or T48H. These group effects clearly

indicate lower ANS activity in SCT carriers, with this reduction reaching about 20 to 50% of the non-carriers' values, depending on the index. The two groups did not differ for SDANN, VLF and LF indices.

3.2.2. Effect of exercise on ANS activity

Exercise decreased SDNN and Ptot in both groups between TR and T24H. Interestingly, a rebound for ANS activity at T48H was observed only for LF and only for the SCT group. This is in contrast with the lack of rebound in parasympathetic activity, as can be observed with the PNN50, RMSSD, and HF indices in the two groups. In addition, exercise did not significantly change RR intervals, SDANN, SDNNIDX, VLF, LF/HF, HFnu or LFnu in either group.

4. Discussion

We mainly observed that SCT carriers were characterized by sympatho-vagal imbalance compared with control subjects at rest and after strenuous exercise, with a deficit ranging from 20 to 50% depending on the HRV parameter.

As already demonstrated, carrying SCT does not alter the ability to practice physical activity at the same level as subjects with normal Hb (Bilé et al., 1998; Gozal et al., 1992; Sara et al., 2003). This was confirmed in the present study by the similar values of VO_{2max} , MAP, HR_{max} and ETD for the two groups.

Resting HRV was lower in SCT carriers in comparison with the control group. This was mainly due to the decreased parasympathetic (i.e., low RMSSD, HF and PNN50) activity (Connes et al., 2006a). SCT carriers had higher LF/HF values than control subjects, confirming marked autonomic imbalance in the former. Altered ANS activity is strongly associated with an increased risk of myocardial infarction, stroke, sudden cardiac death and death from any cause (Dekker et al., 1997, 2000; Ikeda et al., 2007). Indeed, SCT carriers should be considered at greater risk for cardiovascular complications than subjects with normal hemoglobin, as suggested previously (Connes et al., 2006a, 2008).

The risk of sudden death, which is increased during and after exercise in healthy subjects (Albert et al., 2000), is possibly related to acute changes in autonomic tone (Curtis and O'Keefe, 2002). In our

Table 4

Raw values of HRV Fourier analysis in the nocturnal period for both groups before exercise (rest) and 24 and 48 h after exercise (T24H and T48H, respectively)

| | Control group | | | SCT group | | |
|--------------------|---------------|------------------------|----------|-----------|------------------------|----------------------|
| | Rest | T24H | T48H | Rest | T24H | T48H |
| Ptot (ms^2/Hz) | 7363±1154 | 6022±1124 [†] | 7320±997 | 5126±866* | 4186±548* [†] | 4817±430* |
| VLF (ms^2/Hz) | 4080±840 | 3050±846 | 3956±646 | 3186±698 | 2327±428 | 2807±355 |
| LF (ms^2/Hz) | 1114±178 | 1049±159 | 1084±193 | 870±76 | 867±76 | 1062±91 [‡] |
| HF (ms^2/Hz) | 2102±441 | 1844±398 | 2201±501 | 993±311* | 918±183* | 856±118* |
| LFnu | 35.3±4.1 | 37.4±5.6 | 33.4±4.5 | 49.9±5.7* | 48.4±5.2* | 54.0±3.0* |
| HFnu | 64.7±4.1 | 62.6±5.6 | 66.6±4.5 | 50.1±5.7* | 51.6±5.2* | 46.0±3.0* |
| LF/HF | 0.8±0.1 | 0.9±0.2 | 0.7±0.2 | 1.7±0.4* | 1.4±0.3* | 1.7±0.2* |

Values are means±SEM. *Significant difference between groups $P<0.05$; [†] significantly different from rest $P<0.05$; [‡] significantly different from T24H $P<0.05$.

study, exercise did not significantly change SDANN or SDNNIDX but decreased SDNN and Ptot at T24H in both groups. These changes suggest decreased ANS activity 24 h after exercise in both groups, as already reported in other works (Furlan et al., 1993; Hautala et al., 2001). The SCT group was marked by low HRV in resting conditions and exercise did not further decrease this difference with the control group. ANS activity was still lower in the SCT group compared with the control group 24 h after exercise (i.e., lower Ptot, PNN50, RMMSD, HF, HFnu indices and higher LF/HF and LFnu values in SCT carriers). Therefore, the greater risk for cardiovascular complications in SCT carriers, and possibly for exercise-related death (Kark et al., 1987), which is already related to the pre-exercise alterations in sympatho-vagal balance, was always present in the 24 h following exercise.

Strenuous exercise is known to induce a temporary decrease in ANS activity in healthy athletes, followed by a rebound a few hours or days later and reaching 200% after two days of rest (Furlan et al., 1993). Usually, this rebound mainly concerns the parasympathetic indices of ANS activity and is thought to be highly protective against sudden cardiac death (Hull et al., 1994). However, in the present study, a rebound was noted for the SCT carriers only 48 h after exercise and surprisingly concerned mainly the LF index which contains both parasympathetic and sympathetic activities. Whether this phenomenon increase the risk of exercise-related sudden death reported in SCT carriers a few days after exercise remains unknown. Nevertheless, the two groups were not different regarding LF values at any time suggesting a minor role of this component in the post-exercise complications reported in SCT carriers. Despite an increase in the LF index at T48H in SCT carriers, the LF/HF ratio did not increase significantly at that time compared with the resting value. This may be due to the fact that this ratio was already so severely altered at rest (mean value close to 2.0) compared with the value measured in the control group (mean value close to 1.0) that it was not possible to increase the disequilibrium. The lack of parasympathetic activity rebound in the control group is surprising and further studies are needed to find explanations. Urinary or blood stress hormones measurements could be useful for better understanding of the underlying mechanisms.

The reasons for such altered sympatho-vagal balance at rest and after exercise in SCT carriers as compared with subjects with normal hemoglobin are unknown but it was recently suggested that blood rheology could be directly involved in the regulation of cardiac function and activity (Connes et al., 2006a, 2008; Reims et al., 2005; Yokusoglu et al., 2007). Connes et al. (2008) recently reported significant relationship between red blood cell rigidity and PNN50 which supports the hypothesis that ANS equilibrium is affected by perturbations in blood rheology. Moreover, Dintenfass and Lake (1977) reported significant correlations between ECG ST-segment depression and blood viscosity factors, suggesting that blood rheology, again, is involved in the impairment of cardiac activity. Tripette et al. (2007) recently observed the characteristics of blood rheology in response to three repetitions of a ramp exercise test in SCT carriers and a control group. Although RBC rigidity was not significantly different between the two populations at rest, SCT carriers reached significantly higher values for RBC rigidity than control subjects at T24H and T48H. Reduced RBC deformability may adversely affect capillary recruitment and adequate delivery of oxygen to tissues (Parthasarathi and Lipowsky, 1999). Therefore, a decreased parasympathetic activity could be taken as physiologically logical but clinically dangerous ANS response to compensate for the reduction in oxygen availability to tissues in SCT carriers. Indeed, the conjunction of sympatho-vagal imbalance and hemorheological impairment after exercise might constitute a risk for cardiovascular complications in this population at that time.

In conclusion, SCT carriers were marked by lower ANS activity than controls at rest as well as after exercise. Whether or not this sympatho-vagal imbalance suggests a greater risk for cardiovascular

complications in SCT carriers remains unknown and further studies are clearly needed. Fortunately, most of the SCT carriers have no difficulty performing in competitive sports without complications and the overall incidence of sudden death in SCT carriers, as well as in the general population, remains extremely low. Impaired ANS activity alone cannot explain the cases of exercise-related sudden death reported in SCT carriers. However, the ANS impairment in conjunction with other factors, such as hemorheological impairment (Tripette et al., 2007) and extreme climatic conditions such as hypoxia or warm and humid environment (Kark and Ward, 1994), might further increase the risk for cardiovascular disturbances in this population. Larger cohort studies are clearly needed to identify sub-profile of ANS activity in SCT carriers.

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