Acute Moderate Exercise Does Not Further Alter the Autonomic Nervous System Activity in Patients with Sickle Cell Anemia

Mona Hedreville, Keyne Charlot, Xavier Waltz, Stéphane Sinnapah, Nathalie Lemonne, Maryse Etienne-Julan, Valérie Soter, Olivier Hue, Marie-Dominique Hardy-Dessources, Jean-Claude Barthélémy, et al.

To cite this version:
Acute Moderate Exercise Does Not Further Alter the Autonomic Nervous System Activity in Patients with Sickle Cell Anemia

Mona Hedreville1,2,*, Keyne Charlot1,3,4,*, Xavier Waltz1,3,4, Stéphane Sinnapah1, Nathalie Lemonne5, Maryse Etienne-Julian3,5, Valérie Soter6, Olivier Hue1, Marie-Dominique Hardy-Dessources3,4, Jean-Claude Barthélémy7, Philippe Connes1,3,4,8.

1 Laboratory ACTES (EA 3596), Department of Physiology, French West Indies and Guiana University, Pointe-a-Pitre, Guadeloupe, France, 2 Emergency Care Department, Academic Hospital of Pointe-a-Pitre, Pointe-a-Pitre, Guadeloupe, France, 3 UMR Inserm U1134 French West Indies and Guiana University, Pointe-a-Pitre, Guadeloupe, France, 4 Laboratoire d’Excellence du Globule Rouge (LABEX GR-Ex), PRES Sorbonne, Paris, France, 5 Sickle cell Center, Academic Hospital of Pointe-a-Pitre, Pointe-a-Pitre, Guadeloupe, France, 6 Direction of Research and Innovation, Academic Hospital of Pointe-a-Pitre, Pointe-a-Pitre, Guadeloupe, France, 7 Laboratory EA4607 SNA-EPI, Jean Monnet University of Saint-Etienne, PRES Lyon, Saint-Etienne, France, 8 Institut Universitaire de France (IUF), Paris, France

Abstract

A decreased global autonomic nervous system (ANS) activity and increased sympathetic activation in patients with sickle cell anemia (SCA) seem to worsen the clinical severity and could play a role in the pathophysiology of the disease, notably by triggering vaso-occlusive crises. Because exercise challenges the ANS activity in the general population, we sought to determine whether a short (<15 min) and progressive moderate exercise session conducted until the first ventilatory threshold had an effect on the ANS activity of a group of SCA patients and a group of healthy individuals (CONT group). Temporal and spectral analyses of the nocturnal heart rate variability were performed before and on the 3 nights following the exercise session. Standard deviation of all normal RR intervals (SDNN), total power, low frequencies (LF) and high frequencies powers (HF) were lower but LF/HF was higher in SCA patients than in the CONT group. Moderate exercise did not modify ANS activity in both groups. In addition, no adverse clinical events occurred during the entire protocol. These results imply that this kind of short and moderate exercise is not detrimental for SCA patients.


Editor: Xiongwen Chen, Temple University, United States of America

Received December 12, 2013; Accepted March 27, 2014; Published April 16, 2014

Copyright: © 2014 Hedreville et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: KC is funded by a Contrat Plan Etat Région (CPER) grant and XW was supported by a grant from Inserm and the Region Guadeloupe. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: pconnes@yahoo.fr

† These authors contributed equally to this work.

Introduction

Sickle cell anemia (SCA) patients are marked by several biological abnormalities such as decreased red blood cells (RBC) deformability [1–5], increased RBC aggregates strength [2,3,6] and inflammation [7], and a pro-oxidant state [8], which play a role in several complications. However, they are also characterized by an alteration of the autonomic nervous system (ANS) activity (i.e., parasympathetic withdrawal and sympathetic predominance), determined by the analysis of heart rate variability (HRV) in resting condition [9,10], with the degree of alteration reflecting the clinical severity [11–13]. Nebor et al [11] demonstrated that SCA patients at high risk for developing painful vaso-occlusive crises have a large parasympathetic activity withdrawal in comparison with less severe SCA patients. This sympatho-vagal imbalance may further exacerbate vaso-occlusive crises by increasing peripheral vasoconstriction [10].

While regular physical activity has been proven to be a clinical strategy able to decrease co-morbidity and provide health benefits in several chronic diseases such as obesity, diabetes or asthma [14–16] health care professionals have not yet considered a clinical benefit of physical exercise for patients with SCA [17]. Depending on its duration and intensity, exercise may promote lactic acidosis, tissue hypoxia and/or dehydration, which are conditions known to stimulate the polymerization of the abnormal hemoglobin (HbS) and RBC sickling, hence triggering vaso-occlusive events [18]. Nevertheless, few studies demonstrated that exercises lasting less than 30 min at intensity lower than 75% of predicted maximal heart rate (HR) were well tolerated by SCA patients regarding hemorheological, inflammatory, vascular and oxidative stress parameters [19–21]. Moreover, we recently demonstrated that a short (less than 15 min) exercise conducted until the first ventilatory threshold (VT1; moderate intensity) did not cause supplemental alterations in RBC deformability, blood viscosity or coagulation markers in SCA patients [1]. In healthy individuals, exercise is known to challenge the ANS activity with a wide parasympathetic withdrawal during, but also several hours after the effort [22]. Usually, a rebound of the parasympathetic activity is observed two days after an exercise bout, which may confer cardiovascular protection [22]. There is an increasing need to define, in terms of intensity and duration, what kind of exercise...
SCA patients may perform without any risk for developing acute complications. Thus, the aim of this study was to assess the effects of a short (<15 min) and moderate exercise (progressive session conducted until the first ventilatory threshold) on the ANS activity of a group of SCA patients and a group of healthy individuals. Incremental exercise is widely used in several chronic diseases to screen for cardiorespiratory and/or peripheral disorders, as well as to define intensity for training programs, but has been rarely utilized in SCA, and it is unknown whether this classical exercise is safe or not for this population. The demonstration that an incremental exercise conducted to the first ventilatory threshold would be safe for SCA patients could, then, be used to propose individualized exercise rehabilitation program in the near future.

Materials and Methods

Subjects

Seven patients with SCA (4 males and 3 females, age: 33.3 ± 10.8 yrs, weight: 63.0 ± 12.7 kg, height: 173 ± 7 cm, hematocrit: 22.7 ± 4.3%, white blood cells: 9.37 ± 2.13 10^9/l, RBCs: 2.83 ± 0.53 10^{12}/l, hemoglobin concentration: 1.33 ± 0.44 g/dl) and a control group of 9 subjects with normal hemoglobin (CONT; 5 males and 4 females, age: 34.8 ± 8.4 yrs, weight: 75.8 ± 11.8 kg and height: 172 ± 8 cm) agreed to participate in the present study. All the SCA patients recruited were regularly followed by the Sickle Cell Unit of the Academic Hospital of Pointe-à-Pitre (Guadeloupe) and were in steady-state condition at the time of recordings analyzed covers several full sleep cycles including thus a similar repartition of sleep states between subjects. This allows comparison between successive nights and subjects. Artifacts were replaced by the mean of the two neighbors RR. Resulting RR signals are then re-sampled at 2 Hz using a cubic spline interpolation. A temporal analysis of HRV was performed to calculate the standard deviation of all normal RR intervals (SDNN) and the square root of the mean squared differences between adjacent normal RR intervals (RMSSD). After fast Fourier transform (FFT), 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 [25]. The FFT is based on the fact that data present with a stationary organization and are a combination of sinusoidal functions. The low frequencies (LF, 0.04–0.15 Hz) are known to reflect both sympathetic and parasympathetic activities. The high frequencies (HF, 0.15–0.40 Hz) reflect parasympathetic activity. The LF/HF ratio, which was used as a broad index of “sympathovagal balance” [25], and the total frequency power (Ptot) were also calculated. SDNN and Ptot reflected the global autonomic activity, the LF/HF ratio has been proposed as a marker of ANS balance and the RMSSD is strongly related to HF power [28, 29].

Statistics

The results are presented as mean ± standard deviation (SD). The time courses of temporal and spectral indices of HRV were compared between the two groups using a two-way analysis of variance (ANOVA) with repeated measures after log transformation of the data. However, results are presented in absolute value. Pair-wise contrasts were used when necessary to locate where significant differences occurred. The significance level was defined as p<0.05. Analyses were conducted using Statistica (v. 5.5, Statsoft, Tulsa, OK, USA).

Acute Exercise

The exercise protocol has been previously described in details [1]. Briefly, the cycling exercise (Welch Allyn cycloergometer, USA) test, conducted between 1:00 and 3:00 PM, consisted of 3 minutes warm-up at 10 W for SCA and 20 W for CONT, and then, the load was increased every minute (i.e., SCA: 3–7 W; CONT: 15–30 W) until VT1 was reached. The power increment used for SCA patients was close to the one previously used by Callahan et al. [23]. Blood pressure measurements, heart rate and pulse oxymetry monitoring were strictly performed by an experienced cardiologist in the line of the recommendations of the French Society of Cardiology. Gas exchanges were measured with a breath-by-breath automated exercise metabolic system (Oxycon Mobile, Jaeger, Germany) to determine the appearance of VT1 during exercise (see [1]). Pedaling speed remained constant at 60–70 rotation per minute during the exercise test.

Autonomic Nervous System Activity

During the mass of measurement, a holter electrocardiograph (Novacor system, Duosoft, France) was placed on the chest of each patient after clinical examination and recording of the inter-beat (RR) intervals was performed from 6:00 p.m. to 8:00 a.m. RR intervals were visually inspected, corrected if presence of artifacts, then validated before analysis. Only the night periods were analyzed (midnight to 7 a.m.) to avoid variations arising from differences in the subject’s daily environment. HRV recordings during the nights avoid variations due to daily activities, which may vary from one day to another, which would decrease the signal (variations caused by the exercise) to noise (variations due to the daily activities) ratio [24]. The large period of recordings analyzed covers several full sleep cycles including thus a similar repartition of sleep states between subjects.
Results

Statistical analysis revealed that SDNN (group effect: $p = 0.048$), RMSSD (group effect: $p = 0.048$), Ptot (group effect: $p = 0.0502$), LF (group effect: $p = 0.037$) and HF (group effect: $p = 0.05018$) levels were lower and LF/HF levels (group effect: $p = 0.042$) higher in the SCA group than in the CONT group (Table 1; Figure 1). Neither a time effect, nor a time x group interaction was found for all indices (Table 1; Figure 1). Although oxygen uptake, ventilation and power were lower in SCA patients than CONT subjects at VT1 (data not shown, see [1]), HR ($133 \pm 21$ vs $136 \pm 19$ bpm for CONT and SCA, respectively) and mean arterial pressure ($101.2 \pm 13.2$ vs $100.6 \pm 15.6$ mmHg for CONT and SCA, respectively) were similar. Except one SCA individual who exhibited a 11% decrease of hemoglobin oxygen saturation compared to baseline, the other individuals (CONT and SCA) did not exhibit significant (i.e., more than 4%; [1]) change. Using the Borg scale [30] of perceived exertion, SCA patients and controls reported that the feeling of effort, strain, discomfort and/or fatigue was mild to moderate [score ranging from 11 to 13].

Discussion

The aim of the present study was to test the effect of a single moderate (progressive session conducted until the first ventilatory threshold) and short exercise (<15 min) on the ANS activity of SCA patients. The physiological responses indicate that the exercise represented the same relative physiological stress for SCA patients and CONT subjects despite different aerobic capacities. Although two patients of the SCA group exhibited paroxystic and non-severe arrhythmia, the exercise was well tolerated.

Baseline ANS activity has been reported to be altered in SCA patients compared to healthy subjects [9–11], which is in agreement with our findings since all HRV parameters were lower in the SCA group than in the CONT group. Moreover LF/HF levels were higher in the SCA group indicating that the sympathetic activity was predominant due to a parasympathetic withdrawal. The reasons of these differences are not yet fully understood [5]. However, it has been suggested that chronic anemia may lead to a persistent sustained decrease in autonomic fluctuations [29]. Moreover, repeated hypoxic episodes, as it can be the case in SCA patients [31], may increase sympathetic activity and decrease parasympathetic activity [32]. Very short and transient hypoxic stress stimulus has been reported to induce parasympathetic withdrawal in SCA patients but not in healthy individuals [33]. The role of hypoxemia/hypoxia on ANS dysfunction has been reinforced by studies in rats showing that chronic hypoxia causes cell loss in the nucleus ambiguous, a structure from which several vagal efferent axons innervate ganglionated plexuses in the dorsal surface of cardiac atria, which in turn may have different functional roles in cardiac regulation.
bouts, we did not investigate the immediate effects of exercise on ANS activity several hours and days after the exercise could be safely performed in SCA patients with. While we those of Waltz et al. [1], strongly suggest that this kind of exercise with a mild clinical expression of the disease. These results, with importantly did not further alter the ANS activity of SCA patients threshold has no positive impact on ANS activity but most single exercise session performed until the first ventilatory duration (15 min) [37]. In SCA patients, prolonged and intense exercise session usually alters ANS activity within the first night following exercise [22,56]; HF being lower than before the effort. Then, on the second night after the effort, some authors noted a return to baseline of the ANS activity [36] or even a positive rebound of the parasympathetic activity conferring greater cardiac and vascular protection than before exercise [22]. Myllymaki et al. [37] showed, in healthy individuals, that a 90-min exercise session at moderate intensity (60% VO_{2max}) decreased ANS activity on the night following exercise while a 30-min session at high (75% VO_{2max}), moderate or low intensity (45% VO_{2max}) or a 60-min session at moderate intensity had no impact. Indeed, in healthy subjects, exercise duration seems to be more important than intensity to really challenge ANS on the night following exercise, and the absence of ANS activity fluctuations after exercise in the CONT group was probably related to the too short exercise duration (<15 min) [37]. In SCA patients, prolonged and intense exercise bouts are usually dangerous since they may trigger red blood cell sickling and painful vaso-occlusive crises [17]. The lack of change in the ANS activity of SCA patients, which are not involved in any physical activity, after the exercise suggests that the effort proposed 1) is safe and well tolerated by this population (no adverse clinical event occurred during the entire protocol), with no further alterations in ANS activity but, 2) is probably not intense and/or prolonged enough to promote positive autonomic adaptations as it can be the case, sometimes, for healthy subjects [22].

In conclusion, this study shows that a short (<15 min duration) single exercise session performed until the first ventilatory threshold has no positive impact on ANS activity but most importantly did not further alter the ANS activity of SCA patients with a mild clinical expression of the disease. These results, with those of Waltz et al. [1], strongly suggest that this kind of exercise could be safely performed in SCA patients with. While we analyzed the ANS activity several hours and days after the exercise bout, we did not investigate the immediate effects of exercise on

<p>| Table 1. Temporal indices of heart rate variability. |
|------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>D-1</th>
<th>D0</th>
<th>D1</th>
<th>D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONT</td>
<td>CONT</td>
<td>D0</td>
<td>D1</td>
<td>D2</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>SDNN</td>
<td>RMSSD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CONT</td>
<td>CONT</td>
<td>CONT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62.4±10.9</td>
<td>62.2±9.8</td>
<td>61.3±9.7</td>
<td>65.0±16.4</td>
</tr>
<tr>
<td></td>
<td>65.6±5.1</td>
<td>67.8±3.8</td>
<td>69.3±7.0</td>
<td>71.7±5.4</td>
</tr>
<tr>
<td></td>
<td>121±39</td>
<td>106±48</td>
<td>119±33</td>
<td>114±41</td>
</tr>
<tr>
<td></td>
<td>96±28</td>
<td>80±19</td>
<td>87±24</td>
<td>76±18</td>
</tr>
<tr>
<td></td>
<td>74±30</td>
<td>70±44</td>
<td>71±31</td>
<td>69±46</td>
</tr>
<tr>
<td></td>
<td>46±29</td>
<td>39±18</td>
<td>41±24</td>
<td>36±20</td>
</tr>
</tbody>
</table>

Values are mean ± SD. D-1: the night before exercise, D0: the following night after exercise, D1 and D2: the nights 1 and 2 days after exercise, HR: Heart rate, SDNN: standard deviation of all normal RR intervals, RMSSD: square root of the mean squared differences between adjacent normal RR intervals. *Significant group effect (p< 0.05). doi:10.1371/journal.pone.0095563.t001

Acknowledgments

We sincerely thank the Academic Hospital of Pointe-a-Pitre for its financial support. The authors also thank all the subjects who participated in the present study, the nurse (Mrs. Drymon) and Mrs. Lipau.

Author Contributions

Conceived and designed the experiments: MH NL VS MDHD JCB PC. Performed the experiments: MH KW SS NL MDHD PC. Analyzed the data: MH KW SS NL MEJ VS OH MDHD JCB PC. Wrote the paper: MH KW SS NL MEJ VS OH MDHD JCB PC.
References


