How to implement endurance exercise training in sickle cell disease

by Laurent A. Messonnier, Manon Riccetti, Benjamin Chatel, Frédéric Galactéros, Barnabas Gellen, Thomas Rupp, Léonard Féasson, and Pablo Bartolucci

Haematologica 2020 [Epub ahead of print]

Citation: Laurent A. Messonnier, Manon Riccetti, Benjamin Chatel, Frédéric Galactéros, Barnabas Gellen, Thomas Rupp, Léonard Féasson, and Pablo Bartolucci. How to implement endurance exercise training in sickle cell disease.
Haematologica. 2020; 105:xxx
doi:10.3324/haematol.2020.267047

Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in print on a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
LETTER TO THE EDITOR

How to implement endurance exercise training in sickle cell disease.

Laurent A. Messonnier¹, Manon Riccetti¹, Benjamin Chatel², Frédéric Galactéros³,⁴, Barnabas Gellen⁵, Thomas Rupp¹, Léonard Féasson⁶,⁷ and Pablo Bartolucci³,⁴

¹ Université Savoie Mont Blanc, Laboratoire Interuniversitaire de Biologie de la Motricité, EA7424, Chambéry, France.
² CellMade, Le Bourget-du-Lac, France
³ Sickle Cell Referral Center, UMGGR, Hôpital Henri-Mondor (AP-HP), Université Paris-Est Créteil (UPEC), Créteil, France.
⁴ Institut Mondor de Recherche Biomédicale, unité 2, Inserm, Hôpital Universitaire Henri-Mondor, Université Paris-Est Créteil (UPEC), Créteil, France.
⁵ Department of Cardiac Rehabilitation, Henri-Mondor University Hospital, Assistance Publique–Hôpitaux de Paris (AP-HP), Créteil, France.
⁶ Université de Lyon, Université Jean Monnet, Laboratoire Interuniversitaire de Biologie de la Motricité, EA 7424, Saint-Etienne, France.
⁷ Unité de Myologie, Service de Physiologie Clinique et de l’Exercice, Hôpital Universitaire de Saint-Etienne, Saint-Étienne, France.
Corresponding Author:
Laurent A. Messonnier, Ph.D
Université Savoie Mont Blanc, Laboratoire LIBM
Campus Universitaire Savoie Technolac
F-73376 Le Bourget du Lac Cedex, France
Phone: 33 (0) 4 79 75 81 85
e-mail: laurent.messonnier@univ-smb.fr

Running title: Implementation of endurance exercise in SCD

Keywords: Physical activity, lactate, heart rate, exercise intensity
A previous study demonstrated the safety and the beneficial effects of moderate-intensity endurance exercise training in sickle cell disease (SCD) patients. However, this previous pilot study revealed several limitations. The most important constraint was the need for repeated blood lactate concentration measurements to adjust training intensity. This approach considerably hinders implementation and dissemination of endurance exercise training in the general population of SCD patients. In the present study, we tested heart rate as a possible surrogate for adjustment of training intensity. Patients (n = 15) performed successively an initial submaximal incremental test (SIT1), 30-min moderate-intensity cycling exercises 3 times a week for 8 weeks, and finally another SIT (SIT2). Heart rate (HR) and blood lactate concentration ([lactate]b) were recorded every minute during SITs and once during training sessions. [lactate]b and HR values measured during training concurred with the correlation obtained between [lactate]b and HR during SITs. Provided that patients’ individual [lactate]b vs. HR relationship (obtained during a SIT) is known and patients are accustomed to cycling exercise, HR appears to be an acceptable surrogate to control and adjust intensity of endurance exercises.

Sickle cell disease (SCD) is the most frequent genetic disease worldwide. Vaso-occlusion and anemia, the two main consequences of the disease, induce a myriad of complications affecting almost all organs. Physical exercise was until recently considered a risk for SCD patients. Indeed, 31% of vaso-occlusive crises (VOC) and 32% of secondary acute chest syndromes occur subsequent to exertion.¹ However, recent reports provided evidence that when well-calibrated, moderate-intensity endurance-exercise training in adults with sickle-cell disease without severe chronic complications seems safe, significantly improved functional capacity and is a potential novel therapeutic strategy.²,³ Although encouraging, this previous pilot study suffers from several constraints, limiting its scientific and clinical impact: the training program was
relatively short, involved a limited number of patients, was performed on cycle-ergometers in a medical center under the supervision of a physician, and required repeated blood lactate concentration ([lactate]_b) measurements. These limitations hinder implementation and dissemination of long-term endurance exercise training in the general population of SCD patients. The key point was therefore to find non-invasive marker to adjust exercise intensity during endurance training and physical activity in SCD patients. Here we proposed and tested heart rate as the possible surrogate.

Data from 8 men (53%) and 7 women (47%) adult SCD patients (34±11 years, 172±10 cm, 66±11 kg) was analyzed (ClinicalTrials.gov, number NCT02571088). Patients successively underwent a submaximal incremental test (SIT1), an 8-week endurance exercise training program, and a post-training SIT (SIT2). SIT1 and SIT2 started at 20 or 30 W and increased every two minutes by 10 or 15 W for females and males, respectively. Heart rate (HR) and blood lactate concentration ([lactate]_b) were recorded every minute. HR was derived from a 12-lead ECG (ErgoCard, Medisoft, Sorinnes, Belgium). For [lactate]_b, a blood drop (10 µL) was taken from the earlobe and tested extemporaneously within 15-20 s (Lactate Scout+, EKF diagnostics, Cardiff, UK). Exercise was stopped as soon as [lactate]_b was ≥ 4 mmol L^{-1}. HR at the first lactate threshold (LT1) and at 2.5 mmol L^{-1} of [lactate]_b were determined. Three times a week, patients performed 30-min moderate-intensity cycling exercises, for 8 weeks. [lactate]_b and HR were measured during training sessions. Data are mean±SD. HR and [lactate]_b obtained during SIT were correlated using polynomial regressions. Standard errors of the estimate (SEE) to the regression line were calculated.
Figure 1 reports [lactate]_b vs. HR curves (circles) obtained during SIT1 (and SIT2 for patients N and O). Mean R^2 of the [lactate]_b vs. HR polynomial regressions was 0.954±0.056. Mean SEE values to the polynomial regression was 0.555±0.388 mmol·L^{-1}. Figure 1 also reports [lactate]_b and the associated HR measured during the training sessions (triangles). Mean SEE values of [lactate]_b during training to the polynomial regression was 0.714±0.047 mmol·L^{-1}. During training, no patient who displayed HR in the range between LT1 and 2.5 mmol·L^{-1} experienced [lactate]_b \geq 4 mmol·L^{-1}.

The present study aimed to find a surrogate for [lactate]_b to implement and widely disseminate endurance exercise training among SCD patients. If the conditioning strategy is to target an exercise intensity low enough to be safe and elevated enough to induce adaptations, an exercise intensity in between LT1 and 2.5 mmol·L^{-1} [lactate]_b might be targeted.\(^4\) A safety cut off should be set at 4 mmol·L^{-1} since thereafter blood lactate abruptly accumulates and associated acidosis may develop rapidly, especially in SCD.\(^4\) We paid a particular attention to prevent lactate accumulation-associated acidosis, which constitutes a potentially major exercise-related triggering factor of HbS polymerization, sickling and VOC.\(^5\)

A first possibility to implement endurance exercise would be to use the power output (PO) corresponding to a target [lactate]_b obtained during SIT. However, this would oblige patients to exercise on a cycle ergometer so that any other forms of physical activity would be excluded.

A second possibility would be to use heart rate. In thirteen patients, [lactate]_b and the associated HR recorded during training concurred with the correlation obtained during SIT1. In the two remainder patients, we noticed they did not adequately accustom with cycling during SIT1, contrary to the thirteen other patients who rapidly adapted. If data of SIT2 were taken into account for these two patients, the concordance was clear again (figure 1, panels N and O). As a
whole, all HR recorded during training sessions within the LT1 and 2.5 mmol\,L^{-1} window were associated with $[lactate]_b$ close to the target values and never above 4 mmol\,L^{-1} (the safety cut off).

Another possibility would have been to use patients’ RPE. However, sensitivity of RPE appeared (at least in our population) too limited: several patients reported similar RPE for a wide range of PO crossing the LT1-2.5 mmol\,L^{-1} window (figure 2). This large intra- and inter-individual variability may constitute a pitfall in the use of RPE as a mean to precisely manage exercise intensity during training sessions. However, further studies would be necessary to confirm this point.

Taken together, the present data indicate that HR appears to be an acceptable surrogate to implement endurance exercise, as long as patients’ individual $[lactate]_b$ vs. HR relationship (obtained during SIT) is known and patients are accustomed to cycling exercise. To ensure safety and obtain benefit, an exercise intensity objectified by HR ranged between LT1 and 2.5 mmol\,L^{-1} obtained during SIT could be used. Further prospective studies would be needed i) to confirm the accuracy of heart rate as a surrogate for $[lactate]_b$ during endurance training of SCD patients, and ii) to determine the frequency with which SIT must be repeated to take into account the improvements/changes induced by endurance training.
Acknowledgments

This work was supported in part by research funding from “l’association l’ar-mony”.

Authorship

Contribution: L.A.M., F.G., L.F. and P.B. designed and conducted this study. M.R. and B.C. analyzed data. M.R. created the figures. L.A.M. wrote the first draft of the article. All authors critically reviewed the draft and approved the final version for publication.

Conflict-of-interest disclosures

L.A.M. receives/ed gifts and consulting fees from Addmedica and bluebirdbio, respectively. P.B. receives/ed grants and/or consulting fees from Addmedica, bluebirdbio, Emmaus, Fondation Fabre, GBT, Hermanext, Novartis and Roche. All are outside the submitted work.
References


5. Chatel B, Messonnier LA, Bendahan D. Do we have to consider acidosis induced by exercise as deleterious in sickle cell disease? Exp Physiol. 2018;103(9):1213-1220.
Figure Legends

Figure 1: [lactate]_b vs. HR relationship obtained during SIT1 (black circles) and SIT2 for two patients (grey circles, panels N and O), as well as the [lactate]_b–HR pairs measured during the training sessions (open triangles). HR at the first lactate threshold (LT1) as well as at 2.5 mmol·L⁻¹ are also reported (vertical dotted lines).

Figure 2: [lactate]_b vs. HR relationship obtained during SIT1 (black circles) or SIT2 for two patients (grey circles, panels N and O), as well as the RPE values obtained during the same trials (open squares). HR at the first lactate threshold (LT1) as well as at 2.5 mmol·L⁻¹ are also reported (vertical dotted lines).