No Influence of Nonivamide-nicoboxil on the Peak Power Output in Competitive Sportsmen

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ABSTRACT

Recent studies have shown that the oxygenated hemoglobin level can be enhanced during rest through the application of nonivamide-nicoboxil cream. However, the effect of nonivamide-nicoboxil cream on oxygenation and endurance performance under hypoxic conditions is unknown. Therefore, the purpose of this study was to investigate the effects of nonivamide-nicoboxil cream on local muscle oxygenation and endurance performance under normoxic and hypoxic conditions. In a cross-over design, 13 athletes (experienced cyclists or triathletes [age: 25.2 ± 3.5 years; VO_2max 62.1 ± 7.3 mL · min^{-1} · kg^{-1}]) performed four incremental exercise tests on the cycle ergometer under normoxic or hypoxic conditions, either with nonivamide-nicoboxil or placebo cream. Muscle oxygenation was recorded with near-infrared spectroscopy. Capillary blood samples were taken after each step, and spirometric data were recorded continuously. The application of nonivamide-nicoboxil cream increased muscle oxygenation at rest and during different submaximal workloads as well as during physical exhaustion, irrespective of normoxic or hypoxic conditions. Overall, there were no significant effects of nonivamide-nicoboxil on peak power output, maximal oxygen uptake or lactate concentrations. Muscle oxygenation is significantly higher with the application of nonivamide-nicoboxil cream. However, its application does not increase endurance performance.

ABBREVIATIONS

ANOVA	Analysis of variance
F	Nonivamide-nicoboxil cream
Hb	Hemoglobin
HF	Hypoxia-Finalgon
HR	Heart rate
HP	Hypoxia-Placebo
LT	Lactate threshold
LT1	Lactate threshold 1 (first rise)
LT2	Lactate threshold 2 (D_{max})
MPO	Mean power output
NF	Normoxia-Finalgon
NIRS	Near-infrared spectroscopy
NP	Normoxia-Placebo
O_2Hb	Oxygenated hemoglobin
P	Placebo cream
PPO	Peak power output
RER	Respiratory exchange ratio
RPE	Rating of perceived exertion
rel. VO_2	Relative oxygen uptake
smO_2	Saturated muscle oxygenation
SO_2	Arterial oxygen saturation
VO_{2max}	Maximal oxygen uptake
W	Watt

Introduction

During exercise, an enormous increase in blood flow is necessary and O_2 is increasingly extracted from oxygenated hemoglobin (O_2Hb) to meet the oxygen (O_2) demands of the muscle cells [1, 2]. In different conditions, e. g. hypoxia, O_2 supply is a limiting factor of physical performance. With an increase in altitude and a decrease in barometric pressure, a reduction in arterial oxygen partial pressure (pO_2) occurs and thus a drop in O_2 binding to hemoglobin (Hb) [3]. The decrease in O_2Hb leads to a reduced O_2 supply to the muscle cell and, therefore, to reduced performance [4].

It has been shown that the systemic oxygen delivery to the locomotor muscles [5, 6] and the utilization of O_2 in the muscle, depending on capillarization, mitochondrial density, and myoglobin content [7, 8], have a significant influence on endurance peak performance and maximum oxygen uptake (VO_{2max}). However, recent studies also showed that an increased local muscle blood flow, caused by beetroot juice supplementation, can improve performance [9].

The use of a blood circulation-promoting cream (nonivamide-nicoboxil cream: F) could be another way to increase the O_2 supply in the muscles and therefore athletes' performance. As described by Warnecke et al. [10] nonivamide (*N*-Vanillyl-Nonamid) is a synthetic agent related to capsaicin, which leads in combination with esters of nicotinic acid (nicoboxil) to hyperemia after application. The use of a nonivamide-nicoboxil cream increases the O_2Hb level with a simultaneous (but lower) reduction of the deoxygenated hemoglobin (HHb), and thus results in an increase of the total hemoglobin (tHb = HHb + O_2Hb) in the muscle [10]. Earlier radioactive tracer experiments revealed an increase in muscle blood flow through the application of a nonivamide-nicoboxil [11].

However, a lack of research regarding the effects of local blood flow and oxygenation during exercise under hypoxic conditions still exists. Only a few studies have investigated the influence of increased muscular perfusion on O_2 saturation in normoxia [10–12] or focused on the effects of local blood flow and muscle oxygenation on physical performance [12, 13]. Thus, the question arises, whether the vasodilatory effect of F may favor the local muscle oxygenation and increases the performance during normoxic (N) and hypoxic (H) conditions.

Therefore, this study aimed to investigate the effects of an increased local muscle oxygenation on the performance of sportsmen in hypoxia compared to normoxia using F. In addition, we examined the change in systemic and local oxygenation and the O_2 extraction of the muscles under these conditions.

Materials and Methods

Participants

13 male cyclists/triathletes [age: 25.2 ± 3.5 years; height: 180.4 ± 5.2 cm; mass: 71.0 ± 8.0 kg; VO_{2max}: 62.1 ± 7.3 mL $min^{-1} \cdot kg^{-1}$; body fat: 9.3 ± 3.2 %; skinfold thickness: 5.2 ± 1.1 mm; (mean ± SD)] who were experienced with laboratory testing procedures participated in this blinded, randomized, cross over study. The procedures were approved by the local ethics committee and were conducted according to international standards [14]. Each participant was informed about the procedure and protocols, and signed a declaration of agreement. Prior to all testing, the cyclists were not allowed to perform strenuous exercise, and were instructed to refrain from caffeine prior to exercise testing.

Experimental Design

To test the influence of nonivamide-nicoboxil cream (Finalgon cream, Boehringer Ingelheim GmbH & Co. KG, Germany, containing 0.17 % nonivamide and 1.08 % nicoboxil) on local muscle oxygenation, blood lactate concentration, O_2 uptake, and peak power output in normobaric hypoxia (2800 m, 14.8 % F_iO_2) and normoxia (64 m above sea level, 20.9 % F_iO_2), athletes performed four maximal graded exercise tests, within a time frame of 3 weeks and at least four days of recovery in between, on the cycle ergometer either with F or a placebo (Ultra-Sensitive Body Lotion, Alverde Naturkosmetik, dm-drogerie markt GmbH und Co KG, Germany; P) applied on the M. vastus lateralis of both legs.

To ensure an accurate measurement of muscle oxygenation using NIRS, only subjects with a skin thickness < 12 mm were allowed to participate in the study. Athletes' subcutaneous fat thickness at the vastus lateralis was identified using ultrasound (Xario XG, Toshiba, Tokyo, Japan) one week before the first exercise test. Additionally, both creams were applied on the skin to test allergic reactions.

Incremental Step Test

All participants performed four maximal graded exercise tests on cycling ergometer (Schoberer Rad Meßtechnik SRM GmbH, Jülich, Germany) in a randomized order, blinded for H/N and F/P, consisting of cycling at a cadence ≥ 80 revolutions per minute (rpm) with an initial workload of 100 watts (W) and 20 W increments every 3 min (min) until volitional exhaustion. The test was terminated when the cadence decreased below 70 rpm.

Prior to the application of the creams, an area of 18 × 12 cm between patella medialis and the front upper iliac spine was determined and labelled. We wanted to limit the discomfort caused by nonivamide nicoboxil (strong burning sensation on the skin) by limiting the application area. Both creams (F or P) were applied at this determined area on both thighs and covered with a wrapping film. After a 7-min rest period, creams were applied. After a 5-min exposure period, NIRS measurements began, and after an additional 5-min of rest, the incremental step test started.

The hypoxic conditions (2800 m, 14.8 % F_iO_2) were induced by using a normobaric hypoxic-chamber (Hypoxic Training Systems, Hypoxico, New York). The O_2 and CO_2 concentrations were measured during the entire period with a Dräger Multiwarn O_2 and CO_2 gas analyzer (Dräger, Lübeck, Germany). To keep the CO_2 concentration within a physiologically tolerable range (0.03–0.3 %), a CS 2210 CO_2 absorber was used (SK Engineering, Kiel, Germany). To guarantee the blinding during each test, the hypoxic generators were switched on during every condition, but the O_2 concentration was reduced only during the two hypoxic conditions (hypoxia with nonivamide-nicoboxil cream (HF) and hypoxia with placebo (HP)). The temperature and humidity during testing were constant at 21.3 ± 0.1 ° C and 29.3 ± 3.1 %. Independent of the testing conditions (H/N), a 15-min acclimatization phase in the hypoxic chamber was conducted before each exercise testing.

During each test, muscle oxygenation was recorded with a near-infrared spectroscopy (NIRS; Moxy Monitor, wave length: 680 mm – 800 mm, Hutchinson, Minnesota) which was attached to the M. vastus lateralis of both legs and fixed with tape to minimize light reflection and to keep the position. Before each graded exercise test, a 2-min measurement of muscle oxygenation (smO_2) and oxygen uptake (Metalyzer 3B, Cortex Medical, Leipzig, Germany) under resting conditions was performed.

Oxygen uptake, respiratory exchange ratio (RER), and heart rate (HR) (T31, Polar Electro, Kempele, Finland) were averaged over the last 30 s of each step, and capillary blood samples for lactate analysis (EBIOplus, EKF Diagnostic Sales, Magdeburg, Germany) were taken in the last 15 s of each step. To determine lactate concentration, 20 μL of capillary blood was directly mixed with 1 mL of the EBIO plus system hemolysis solution, and analyzed via an amperometric-enzymatically procedure using EBIOplus (EKF Diagnostic Sales, Magdeburg, Germany). At the same time points, the rating of perceived exertion (RPE) was assessed using the 6- to 20-point Borg scale (Borg 1970). Furthermore, arterial oxygen saturation (SO_2) was recorded continuously at the fingertip with a pulse oximeter (Philips C3 Patient Monitor, Amsterdam, Netherlands). During each test, participants did not receive any feedback about the current power output or the total duration. After volitional exhaustion, a visual analog scale was used to assess the pain in leg muscles, and subjects were asked to evaluate the testing condition (H or N).

To compare the different testing conditions, peak power output during NP (PPO_{NP}) was set at 100 %. Afterwards, parameters were compared at rest (R), at 50 %, and 75 % of the $PPO_{NP.}$

Values at physical exhaustion (100 %) during each condition were also compared irrespective of different workloads. Lactate thresholds have been determined using the method of Bishop et al. [15] (D_{max}).

Statistical analysis

Data were tested for normality with the Kolmogorov-Smirnov test with Lilliefors-correction. To assess the differences between the different testing conditions (NP, NF, HP, HF), a two-way analysis of variance [“altitude (oxygen concentration)” (N, H); “cream” (P, F)] repeated-measures ANOVA with Bonferroni post-hoc test was used for each power output separately (R, 50 %, 75 %, 100 %). Descriptive statistics are expressed as means ± standard deviation (SD). All statistical analyses were performed using the software Statistica (Statistica for Windows, Version 7.0., StatSoft, Tulsa, USA).

Results

▶ **Table 1** shows the peak power output (PPO), maximal relative oxygen uptake (rel. VO_{2max}), and maximal heart rate (HR_{max}) of the different conditions. No significant differences in PPO, rel.VO_{2max} and HR_{max} were present between F and P during N or H.

PPO

Over-all ANOVA (analysis of variance) revealed a significant effect of “altitude” on PPO ($p < 0.001$), no significant effect of “cream” on PPO, and no significant interaction effect for any of the conditions (“altitude” * “cream”). Hypoxia significantly decreased PPO.

HRmax

The overall ANOVA revealed no significant effect of “altitude” on HRmax, no significant effect of “cream” on HRmax, and no significant interaction effect for any of the conditions (“altitude” * “cream”).

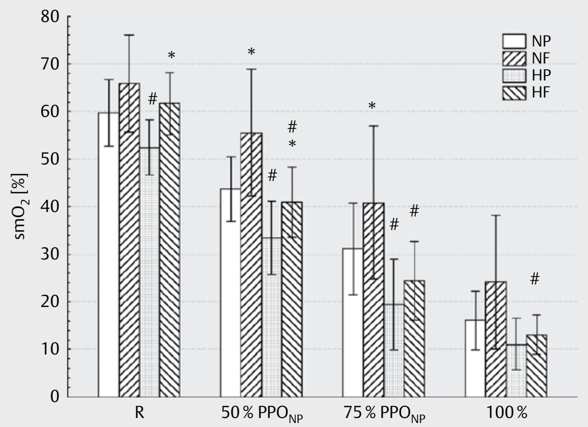
Saturated muscle oxygenation (smO_2)

The overall ANOVA revealed a significant effect of “altitude” on smO_2 under resting conditions ($p < 0.001$), at 50 % ($p < 0.001$) and 75 % ($p < 0.001$) of PPO_{NP} and at 100 % ($p < 0.01$), a significant effect of “cream” on smO_2 under resting conditions ($p < 0.001$), at 50 % ($p < 0.001$) and 75 % ($p < 0.01$) of PPO_{NP} and at 100 % ($p < 0.01$), but no significant interaction effect for any of the conditions (“altitude” * “cream”). smO_2 was reduced by hypoxia and increased by cream at the different workloads (▶ **Fig. 1**).

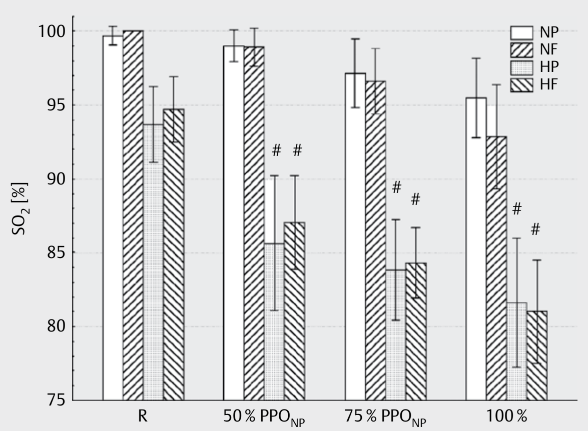
▶ **Table 1** Results of the incremental exercise test during different conditions.

	PPO [W]	VO_{2max} [$mL \cdot min^{-1} \cdot kg^{-1}$]	HR_{max} [min^{-1}]
NP	307 ± 35	62.1 ± 7.3	181 ± 10
NF	313 ± 33	62.0 ± 6.3	181 ± 11
HP	274 ± 28#	52.8 ± 4.7#	180 ± 9
HF	278 ± 31#	53.7 ± 5.8#	180 ± 9

PPO: peak power output, VO_{2max}: maximal oxygen uptake, HR_{max}: maximal heart rate. # significantly different compared with normoxia when using the same cream ($p < 0,05$). Data are shown as mean ± SD.



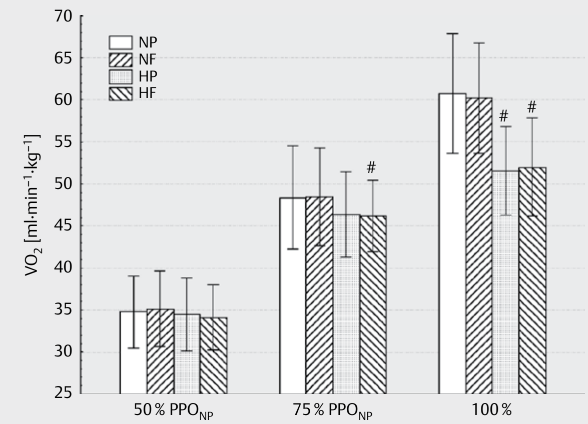
▶ **Fig. 1** Saturated muscle oxygenation (smO_2) under resting conditions, at 50 % and 75 % of the peak power output at normoxia placebo (PPO_{NP}) and after exhaustion (100 %) in each condition * significantly different between different creams at the same altitude (NP vs. NF & HP vs. HF). #significantly different between hypoxia and normoxia when using the same cream (NP vs. HP & NF vs. HF) ($p<0.05$). Data are shown as mean ± SD. NP: Normoxia Placebo; NF: Normoxia Finalgon; HP: Hypoxia Placebo; HF: Hypoxia Finalgon.



▶ **Fig 2** Arterial oxygen saturation (SO_2) under resting conditions, at 50 % and 75 % of the peak power output at normoxia placebo (PPO_{NP}) and after exhaustion (100 %) in each condition. #significantly different between hypoxia and normoxia when using same cream (NP vs. HP & NF vs. HF) ($p<0.05$). Data are shown as mean ± SD. NP: Normoxia Placebo; NF: Normoxia Finalgon; HP: Hypoxia Placebo; HF: Hypoxia Finalgon.

Arterial oxygen saturation (SO_2)

The overall ANOVA revealed a significant effect of "altitude" on SO_2 at 50 % ($p<0.0001$), and 75 % ($p<0.001$) of PPO_{NP} and at 100 % ($p<0.001$), a significant effect of "cream" on SO_2 at 100 % ($p<0.05$), but no significant interaction effect for any of the conditions. SO_2 was reduced by hypoxia and reduced by F at the before mentioned workloads (▶ **Fig. 2**).



▶ **Fig 3** Rel. Oxygen uptake (VO_2) during the different conditions at 50 % and 75 % of the peak power output at normoxia placebo (PPO_{NP}) and after exhaustion (100 %) in each condition. Data are shown as mean ± SD. #significantly different between different altitudes when using the same cream (NP vs. HP & NF vs. HF) ($p<0.05$). NP: Normoxia Placebo; NF: Normoxia Finalgon; HP: Hypoxia Placebo; HF: Hypoxia Finalgon.

Oxygen uptake (VO_2)

The overall ANOVA revealed a significant effect of altitude on VO_2 at 75 % of PPO_{NP} ($p<0.001$) and at 100 % ($p<0.001$), but no significant effect of "cream" on VO_2 for any of the time points and no significant interaction effect for any of the conditions. VO_2 was reduced by hypoxia at the before mentioned workloads (▶ **Fig. 3**).

Lactate

The overall ANOVA revealed a significant effect of altitude on lactate concentration at 50 % ($p<0.001$), 75 % ($p<0.001$) of $PPO_{NP,}$ and at 100 % ($p<0.01$), but no significant effect of "cream" on lactate concentration at any of the time points and no significant interaction effect for any of the conditions. Hypoxia significantly increased lactate levels at different workloads (▶ **Table 2**).

Lactate Threshold (LT)

The overall ANOVA revealed a significant effect of "altitude" on lactate threshold 1 (LT1) and lactate threshold 1 (LT2) ($p<0.001$), but no significant effect of "cream" on LT1 ($p=0.17$) and LT2 ($p=0.93$), and no significant interaction effect for any of the conditions. Hypoxia significantly decreased workload at LT1 and LT2 (▶ **Table 2**).

Visual Analog Scale (VAS)

The overall ANOVA revealed no significant effect of "altitude" on muscular and cardiopulmonal exertion ($p=0.11$, $p=0.11$), no significant effect of "cream" on muscular and cardiopulmonal exertion ($p=0.15$, $p=0.57$), and no significant interaction effect for any of the conditions.

Rating of Perceived Exertion (RPE)

The overall ANOVA revealed no significant effect of "altitude" ($p=0.39$) on RPE, no significant effect of "cream" on RPE ($p=0.39$), and no significant interaction effect for any of the conditions.

▶ **Table 2** Lactate concentration at 50 and 75 % of the PPO_{NP} and after exhaustion (100 %) and LT1 and LT2 in each condition.

	50 % PPO_{NP} [$mmol \cdot L^{-1}$]	75 % PPO_{NP} [$mmol \cdot L^{-1}$]	100 % [$mmol \cdot L^{-1}$]	LT1 (first rise) [W]	LT2 (d_{max}) [W]
NP	1.1 ± 0.7	2.8 ± 1.2	9.8 ± 2.0	198 ± 40	259 ± 41
NF	1.2 ± 0.8	2.8 ± 1.6	9.3 ± 2.5	200 ± 43	257 ± 51
HP	1.8 ± 0.9#	5.9 ± 2.1#	12.0 ± 3.2#	155 ± 30#	223 ± 28#
HF	1.8 ± 0.9#	5.0 ± 2.3#	11.7 ± 1.9#	165 ± 27#	227 ± 32#

NP: Normoxia Placebo; NF: Normoxia Finalgon; HP: Hypoxia Placebo; HF: Hypoxia Finalgon. PPO_{NP}: peak power output during normoxia placebo, LT1: lactate threshold 1, LT2: lactate threshold 2. # significantly different between hypoxia and normoxia when using the same cream (NP vs. HP & NF vs. HF) ($p < 0.05$). Data are shown as mean ± SD.

Discussion

The present study aimed to identify the effects of the application of F on local muscle oxygenation and O_2-extraction of the muscles, the mechanical peak power output, and the systemic oxygenation during exercise under hypoxic and normoxic conditions. The main findings of the present study are a significant increase of smO_2 from the application of F at 50 % of PPO_{NP} in hypoxia and normoxia, and at 75 % of PPO_{NP} under normoxia compared to P. However, no significant effect on PPO, lactate concentrations, and rel.VO_{2max} has been shown, neither in hypoxia nor in normoxia. A significant difference between the effects of hypoxia and normoxia was found for almost all parameters.

In the present study, the application of F led to a significantly higher ($p < 0.01$) smO_2 during hypoxia at rest (HF) and submaximal intensities (50 % and 75 % of PPO_{NP}). As mentioned in the introduction, the physiological mechanisms induced by the application of F are not yet sufficiently clarified [10]. The results of the present study are in line with the results of Warnecke et al. [10] who showed an increased O_2Hb and O_2-saturation in the region cruris posterior above of the M. gastrocnemius and M. soleus after the application of F under resting conditions. In contrast, Zinner et al. [12] detected no increase of O_2 saturation in the M. vastus lateralis. The different results could be due to the fact that Zinner et al. [12] applied F immediately after a 3-min warm-up followed by a baseline measurement. As known, physical activity leads to higher metabolic work and increased muscle blood flow [16] to cover the O_2-demands [2], which may have already led to expanded resting/baseline values. In contrast to Zinner et al. [12], athletes in the present study and the study by Warnecke et al. [10] did not warm up before the rest measurement with the application of F to exclude possible preloads and an increased blood flow.

Concerning performance, results are in line with previous studies. Even though performance tests and exercise time differ markedly, the results are in line with the study of Zinner et al. [12], who also found no significant increase in performance in a 4 km time trial (TT) from the application of F. The results of Zinner et al. [12] showed a mean power output (MPO) of 325 ± 59 W from the application of F, which was similar to the MPO during P (326 ± 60 W) and control (no cream) (321 ± 60 W). However, as the application of F led to a significantly higher smO2 at submaximal intensities (50 % and 75 % of PPO_{NP}), the question arises whether performance could be sustained longer for continuous workloads at submaximal intensities with the application of F.

Generally, the results concerning the influence of hypoxia on performance are in line with the previous literature. Peltonen et al. [17] indicated a significant decrease of PPO (− 12.8 %) in hypoxia (~2800 m, 15.0 % FiO2) compared to performance in normoxia. These findings are comparable to the present results, where the application of F in H led to a decrease of PPO of 11.2 % while using the P led to a drop of 10.7 %

VO_{2max} is considered to be limited by various factors including pulmonary diffusion capacity, cardiac output, O_2 transport capacity, and skeletal muscles [18]. Here, even though a higher smO_2 by the topical application of F was measured, it did not significantly influence VO_{2max}, neither in N nor in H. Saltin and Calbet [5] pointed out that the VO_{2max} is limited by the systemic O_2-transport into the muscles. This finding by Saltin and Calbet [5] is supported by the present study. Despite a significantly increased local muscle oxygenation and thus an increased O_2-supply, there was no significant increase in VO_{2max}. These findings suggest that the increased O_2 availability in the muscle could not be utilized. However, it has to be mentioned, that the area where the cream was applied was perhaps too small to elicit changes in VO_2max or performance, which is a clear limitation of our study.

Conclusion

During submaximal intensities in normoxia (50 % and 75 % PPONP) and hypoxia (50 % PPONP) muscle oxygenation of the M. vastus lateralis was significantly increased through the application of F compared to P. However, the topical application of F prior to an incremental step test does not affect peak power output, arterial oxygen saturation or oxygen uptake of experienced cyclists, showing that the increased O_2 availability in the muscle cannot be utilized.

Conflict of Interest

The authors declare that they have no conflict of interest.

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