Intermittent Hypoxic Training in Endurance Athletes

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FINAL REPORT

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INTRODUCTION

Historically altitude training typically involved athletes living and training at moderate to high altitude (1800-3500) for 2-3 weeks (Billings *et al.*, 1971; Smith & Sharkey, 1984; Fox *et al.*, 1989). However, it soon became apparent that training at such altitudes might actually reduce performance, probably through the increased alkalinity of the blood caused by increased ventilation rates (Jackson & Sharkey, 1988), reduction of plasma volume and loss of muscle mass (Favier *et al.*, 1995). To avoid these disadvantages at high altitude the live-high train-low procedure has become popular with athletes and coaches (Levine & Stray-Gundersen, 1992). Living at moderate altitude and training closer to sea level allows beneficial adaptations due to reduced availability of oxygen to occur, while maintaining training quality. The live-high train-low approach has produced increases of approximately 1-2% in endurance performance (Levine & Stray-Gundersen, 1997; Stray-Gundersen & Levine, 1998), 5% in red blood cell mass, 9% in haemoglobin and 2-4% in maximal oxygen uptake (Levine & Stray-Gundersen, 1997; Stray-Gundersen & Levine, 1998), while other studies have found little or no beneficial effects (Adams *et al.*, 1975; Jensen *et al.*, 1993; Bailey *et al.*, 1998).

Generally due to the difficulties and expense associated with taking athletes to training camps at altitude a number of new devices, which aim to simulate the physiological effects of altitude have recently become available. Altitude simulation involve devices that either decrease the pressure of the inspired air reducing the availability of oxygen to the tissues (hypobaric chamber) or reduces the concentration of oxygen in the inspired air by diluting it with extra nitrogen (altitude tents, hypoxicator machines). These simulation devices have given rise to a number of new procedures that aim to improve athletic performance. One such procedure trialed originally by Russian aviators (Meerson, 1973) is termed intermittent hypoxic training (IHT), which involves the delivery of a number of short bursts of low oxygen air equivalent to high altitude (3000-6000m) interspersed with recovery periods of normoxic air.

IHT has been found to significantly increase erythropoietin (Eckardt *et al.*, 1989; Knaupp *et al.*, 1992), and other red cell parameters (Hellemans, 1999; Rodriguez *et al.*, 2000; Hendriksen & Meeuwsen, 2003). Previous work by our research group found significant improvements in maximal oxygen uptake and haematological variables as well as improved 3000-m running and 1500-m swimming performance after 20 days of IHT (Hellemans, 1999). While other investigators have found similar haematological and performance enhancements using IHT at rest (Rodriguez *et al.*, 1999; Rodriguez *et al.*, 2000) or during exercise (Terrados *et al.*, 1988; Hendriksen & Meeuwsen, 2003) some authors have reported no significant changes in either haematological parameters or athletic performance (Vallier *et al.*, 1996; Frey *et al.*, 2000). Many of the previous studies investigating IHT however have suffered from low subject numbers (Terrados *et al.*, 1988; Vallier *et al.*, 1996) or lack of a control group (Hellemans, 1999; Frey *et al.*, 2000; Rodriguez *et al.*, 2000). The purpose of this study was to conduct a double-blind randomised controlled trial with sufficient subject numbers to determine the effect of IHT on 3-km time trial performance and blood parameters in well-trained multi-sport athletes and to determine any differences between responders and non-responders.

METHODS

Subjects

Twenty-two multi-sport endurance athletes (13 males aged 30 ± 8 years and 9 females aged 35 ± 9 years) were recruited from a local training club. Due to other commitments or low iron levels (Ferritin < 20 $\mu g.L^{-1}$) 4 athletes were replaced prior to the start of the study. Subjects were serious or elite age-group multi-sport endurance athletes in the middle of their training season. All athletes lived at sea level and had not stayed at altitude for longer than 1 week over the past 6 months. Informed voluntary written consent was obtained from each subject prior to the start of the study and the study had the approval of the Lincoln University Human Ethics Committee (reference 2001/24).

Study Design

The study was a double-blind randomised controlled trial. Subjects performed four 3-km time trials including a familiarization, baseline and two post-exposure time trials. The baseline trial was performed 2 weeks after the familiarization trial and one day prior to beginning IHT and placebo exposures. The post-exposure time trials were completed 2 and 17 days after IHT or placebo exposure finished. The IHT group received 90 min of intermittent normobaric hypoxic exposure, while the control group received 90 min of placebo exposure for an average of 15 days over a 3-week period. Blood tests were taken 2 weeks before, 2 and 12 days after IHT and placebo exposure. From the baseline blood tests subjects with very low Ferritin concentrations (< 20 $\mu g.L^{-1}$) were excluded from the study (n = 3), while subjects with low Ferritin concentration (20-30 $\mu g.L^{-1}$) (n = 6) were given iron supplementation to facilitate erythropoiesis. The iron supplement (Healtheries Iron & Vitamin C, Auckland), contained 170mg ferrous glucomate and 40mg ascorbic acid. Subjects were told to take 2 tablets twice a day. Subjects with normal Ferritin concentrations did not receive the iron supplement (n = 16).

Training and Subjective Rating

Subjects were asked to perform maintenance training only during the study period and to refrain from strenuous physical activity 24 hours prior to the performance tests. Subjects were also asked to record their daily training information as well as record their subjective ratings of stress, fatigue, muscle soreness, quality of sleep and their training performance.

Hypoxic and Placebo Treatment

Subjects were randomly assigned in a double-blind fashion to the intermittent hypoxic training group (IHT) (n = 12) or the control group (placebo) (n = 10). For 3 weeks the IHT and placebo group breathed through a hand-held facemask for a total of 90 $min.day^{-1}$ on an average of 5 days per week. For the IHT group intermittent breathing was administered in a ratio of 5 min hypoxic air followed by 5 min ambient air, however for the placebo group the hypoxic air was substituted for ambient air. Subjects were asked to refrain from training for 2 hours before and after the treatment. All subjects completed at least 4 treatment sessions per week. Subjects received either a normobaric hypoxic gas (IHT group) or normal ambient air (placebo group) via the GO_2Altitude® hypoxicator device (Biomedtech, Victoria, Australia). The oxygen concentration in the hypoxic gas was progressively reduced in the IHT group (F_IO_2 = 13% day 1-2, 12% day 3-5, 11% week 2, 10% week 3). Subjects were continually monitored throughout the breathing sessions and if a subject felt light-headed or

unwell during the hypoxic breathing they were instructed to remove the mask and breathe normal room air until they felt well enough to continue. Peripheral oxygen saturation for each individual was monitored either automatically by the hypoxicator device or manually by a research assistant (Sport-Stat, Nonin Medical, Minneapolis, MN).

Performance Test
Performance was assessed by individual 3-km time trials on a 400 m synthetic outdoor running track. Time trials were performed at approximately the same time of day for each individual and in the same order. A warm-up and stretch (10-15 min) was completed before and after each time trial. Before each time trial subjects were instructed to try and achieve the best time possible. Heart rates monitors (Sport Tester, Kempele, Finland) were fitted to each subject prior to each time trial and the average heart rate during the time trial and the recovery heart rate 20 sec after the time trial were calculated.

Blood Measurements
Immediately after each time trial blood lactate concentration from a finger-prick sample was analysed using the YSI 1500 portable lactate analyser (Yellowsprings, Ohio). Subjects were also asked to visit an independent professional testing laboratory (Southern Community Laboratories, Christchurch, New Zealand) for venous blood samples to be taken for determination of haemoglobin concentration, hematocrit, reticulocytes, white-cell count (XE-2100, Sysmex, Japan) ferritin concentration, and serum iron (917, Hitachi, Japan). Subjects were asked to report to the blood laboratory prior to breakfast at approximately the same time each day of the blood tests.

Hypoxic Test
On four occasions all subjects underwent a 10-min hypoxic test where they were asked to breathe normobaric hypoxic air (F_IO_2 = 11%) for 5 min followed by a 5-min recovery period where they breathed normal ambient air. A familiarization hypoxic test occurred 2-weeks prior to the start of the study followed by 10-min hypoxic tests at 8 days before and 1 and 22 days after the exposure period. The familiarization 10-min hypoxic test occurred after the first blood test. During the test peripheral oxygen saturation was monitored and the time taken for subjects arterial oxyhaemoglobin saturation to reach 83% (Td) was recorded along with each subject's lowest oxyhaemoglobin saturation level ($SpO_{2minimum}$).

Statistical Analysis
Changes in the mean of the variables and standard deviations representing the between- and within-subject variability were estimated using a mixed modelling procedure (Proc Mixed) in the Statistical Analysis System (SAS Institute, Cary NC). The same procedure provided 95% confidence limits (the likely range of the true value) for all estimates. We analysed the natural logarithm of each measure to reduce any effects in nonuniformity of error and to obtain changes in measures and errors as percentages. The fixed effects were trial (pre, post1 post2), group (IHT, placebo) and their interaction. The random effects were subject variance, residual variance, and additional within-subject variance for the two post-exposure trials combined for the IHT group. Chances that the true effects were substantial was estimated with a spreadsheet (Hopkins, 2002), when a value for the smallest worthwhile effect is entered. For performance in the 3-km time trial we chose 0.5% as the smallest change

that can affect performance (Hopkins & Hewson, 2001). For the physiological variables we expressed the effects as fractions of the baseline between-subject standard deviation and chose the smallest worthwhile value of this statistic as 0.2 (Cohen, 1988).

RESULTS

Subject Characteristics

The subjects in the two groups were similar in age, height, weight and competitive level, however due to a number of withdrawals and a lack of back-up volunteers the two groups became unmatched for sex (Table 1).

Table 1. Subject characteristics in the placebo and intermittent hypoxic training groups.

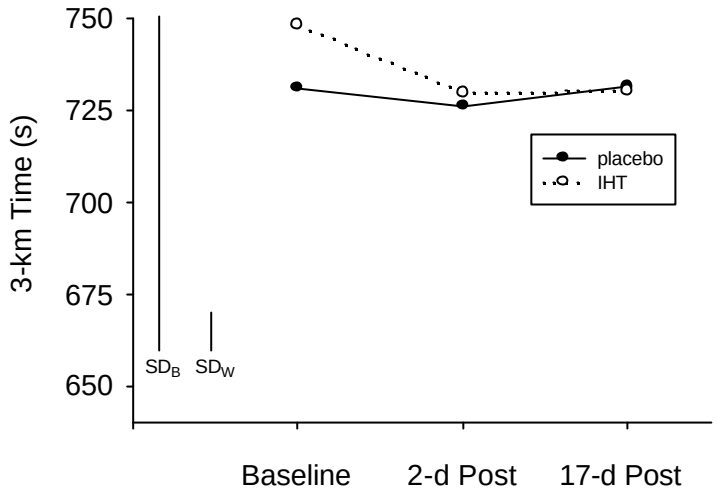
	Placebo	IHT
Competitive level		
National age-group representative	1	1
Serious age-group representative	8	10
Novice	1	1
Age (y)	32.1 ± 9.8	32.3 ± 9.7
Weight (kg)	73.7 ± 11.5	70.1 ± 11.5
Height (m)	1.7 ± 0.1	1.7 ± 0.1
Resting heart rate (min^{-1})	53 ± 6	56 ± 8
Sex	8 male 2 female	5 male 7 female

Data other than sample size and sex are mean ± between-subject standard deviation.

Performance

Compared to baseline performance subjects that were given 3 weeks simulated altitude via IHT improved their 3-km time trial performance by 2.3% (95% Confidence Interval = 0.6-3.9%) 3 days, and 2.2% (0.6-3.9%) 17 days after the last hypoxic episode (Figure 1). Out of the 12 athletes that were given the IHT, 7 had an improved performance (> the smallest worthwhile effect of 0.5%) by the end of the exposure period, which increased to 9 (75%) by the end of the 17-day recovery period. In contrast, relative to baseline the placebo group improved performance by only 0.6% (-1.0 to 2.2%) 3 days and 0.1% (1.6 to -1.3%) 17 days after the treatment. Out of the 10 athletes that were in the placebo group 6 showed an improved performance by the end of the exposure period, but this number dropped to 5 (50%) by the end of the recovery period. The observed standard (typical) error of measurement for 3-km performance in the IHT group was 2.3% (1.6-3.9%) between trials 1 and 2 and 1.6% (1.1-2.7%) between trials 2 and 3. Standard errors for the placebo group were 1.7% (1.2-3.4%) between trials 1 and 2 and 1.0% (0.7-1.9%) between trials 2 and 3. The standard deviation representing individual variation in the change in performance of the IHT group for trials 2 and 3 combined was 1.5%.

Figure 1. Change in mean 3-km time trial performance in placebo and IHT training groups.



Values are means; bars are the standard deviations between subjects (SD_B) and within a subject (SD_W).

Table 2 shows the mean changes in 3-km performance for the placebo and IHT groups, and the statistics for the difference in the changes. It is very likely that the true change in performance after IHT is substantial and unlikely to be trivial.

Table 2. Mean changes in 3-km performance at 2 and 17 days post IHT and placebo exposures, and the chances that the true difference in the changes is substantial.

	Change in performance (%)				Chance that the true difference is substantial[a]	
	IHT	Placebo	Difference ± 95% CL	P	%	Qualitative
2-d post	-2.3	-0.6	-1.7 ± 2.3	.14	85	Likely
17-d post	-2.2	0.1	-2.3 ± 2.1	.03	96	Very likely

[a]Substantial is an improvement in performance of > 0.5%. P: p value.
± 95% CL: add and subtract this number to the mean effect to obtain the 95% confidence limits for the true difference.

Physiological variables

Table 3 shows the change in physiological variables taken during or immediately after the time trial. Blood lactate concentration after the 3-km time trial decreased by ~ 6% in the IHT relative to the placebo group on day 2 after exposure and by ~ 8% on day 17. Substantial decreases resulting from IHT were possible for mean heart rate during the time trial at 2 and 17 days post exposure. It is also possible that IHT resulted in faster recovery of heart rate after the time trial.

Table 3. Mean changes in physiological parameters during or after performance test at 2 and 17 days post IHT and placebo exposures, and the chances that the true difference in the changes is substantial.

	Days post-exposure	Change in measure				Chance that the true difference is substantial[a]	
		IHT	Placebo	Difference ± 95% CL	P	%	Qualitative
Post-test lactate (%)	2	7.0	12.9	-5.9 ± 18.0	.51	51	Possible
	17	-2.4	5.6	-8.1 ± 17.7	.36	61	Possible
Mean heart rate (min^{-1})	2	-1.4	1.9	-3.4 ± 6.1	.26	73	Possible
	17	-2.0	-0.6	-1.3 ± 5.8	.65	46	Possible
Recovery heart rate (min^{-1})	2	0.5	-6.4	6.9 ± 12.6	.27	72	Possible
	17	0.7	-6.5	7.3 ± 12.5	.24	74	Possible

Changes in physiological parameters are in beats per minute (min^{-1}) for heart rates and % for blood lactate concentration. Recovery heart rate; heart rate 20 sec after the time trial ended.

[a]Chances for a substantial decrease in heart rate and blood lactate where substantial is 0.2 of the baseline between-subject standard deviation for each measure.

± 95% CL: add and subtract this number to the mean effect to obtain the 95% confidence limits for the true difference.

Blood variables

Table 4 shows the change in blood variables after the IHT or placebo exposure. Substantial increases resulting from IHT were unlikely for haemoglobin at day 2 but possible by day 12 after exposure. However, substantial increases resulting from IHT in hematocrit and reticulocytes were much more likely. Substantial decreases resulting from IHT exposure were highly likely for serum iron and possible for ferritin. Effects of IHT on mean cell volume and mean cell haemoglobin were trivial.

Table 4. Mean changes in blood parameters 2 and 12 days post IHT and placebo exposures, and the chances that the true difference in the changes is substantial.

	Days post-exposure	Change in measure (%)				Chance that the true difference is substantial[a]	
		IHT	Placebo	Difference ± 95% CL	P	%	Qualitative
Hemoglobin (%)	2	-0.9	-1.1	0.2 ± 3.2	.90	23	Unlikely
	12	-0.7	-3.2	2.5 ± 4.2	.23	70	Possible
Hematocrit (%)	2	-0.8	-2.3	1.5 ± 3.1	.44	78	Likely
	12	-0.6	-4.2	3.6 ± 4.1	.08	96	Very likely
Mean Cell Volume (%)	2	-0.3	0.1	-0.4 ± 0.8	.31	1	Almost certainly not
	12	-0.5	-0.4	-0.1 ± 0.9	.83	6	Unlikely
Mean Cell Hemoglobin (%)	2	0.1	0.6	-0.5 ± 1.1	.37	2	Very unlikely
	12	-0.8	0.7	-1.5 ± 1.4	.04	1	Almost certainly not
Reticulocytes (%)	2	4.2	-19.3	23.5 ± 21.1	.03	97	Very likely
	12	10.7	-3.9	14.6 ± 21.7	.18	87	Likely
White Cells (%)	2	-6.5	-9.5	3.0 ± 15.9	.70	64	Possible
	12	-1.6	-19.2	17.6 ± 16.8	.04	98	Very likely
Serum Iron (%)	2	-23.5	22.3	-45.8 ± 38.2	.02	98	Very likely
	12	-61.9	18.5	-80.4 ± 41.8	.01	99	Almost certain
Ferritin (%)	2	-6.7	10.2	-16.9 ± 19.7	.09	67	Possible
	12	-14.4	-4.5	-9.9 ± 21.2	.35	40	Possible

[a]Chances for a substantial change in blood parameters, where substantial is 0.2 of the baseline between-subject standard deviation for each measure.

± 95% CL: add and subtract this number to the mean effect to obtain the 95% confidence limits for the true difference.

10-min Hypoxic Test

The time taken for subject's arterial oxyhaemoglobin saturation to reach 83% (Td) and subject's lowest oxyhaemoglobin saturation level ($SpO_{2minimum}$) during the hypoxic test was not significantly different between the placebo and IHT groups at baseline. After IHT, arterial oxyhaemoglobin levels did not desaturate to the same extent during the 10-min hypoxic test. IHT subject's $SpO_{2minimum}$ was 5.3% (day 1) and 3.1% (day 22) higher than baseline levels compared to the placebo groups 1.7% improvement on both post-exposure days. IHT groups Td also improved after hypoxic exposure, however the difference was not significant and there is only a possible chance that the true effect is substantial.

Table 5. Mean changes in the time course of the arterial oxy haemo globin saturation during the 10-min hypoxic test at 1 and 22 days post IHT and placebo exposures, and the chances that the true difference in the changes is substantial.

	Days post-exposure	Change in measure (%)				Chance that the true difference is substantial[a]	
		IHT	Placebo	Difference ± 95% CL	P	%	Qualitative
$SpO_{2minimum}$ (%)	1	5.3	1.7	3.6 ± 5.7	.22	80	Likely
	22	3.1	1.7	1.4 ± 6.2	.65	54	Possible
Td (%)	1	19.3	12.3	7.0 ± 50.5	.78	48	Possible
	22	15.7	4.7	11.0 ± 53.7	.68	54	Possible

$SpO_{2minimum}$; the minimum arterial oxy haemoglobin saturation reached during the 10-min hypoxic test, Td; time taken for SpO_2 to reach 83%.

[a]Chances for a substantial increase in SpO_2 and Td where substantial is 0.2 of the baseline between-subject standard deviation for each measure.

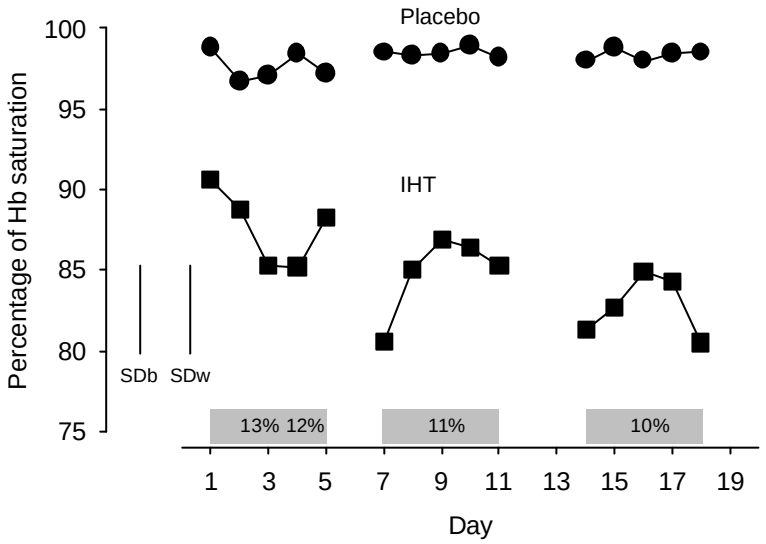
± 95% CL: add and subtract this number to the mean effect to obtain the 95% confidence limits for the true difference.

Values for $SpO_{2minimum}$ and Td from the first 10-min hypoxic test in IHT subjects was correlated with subsequent performance at 2 and 17 days post hypoxic exposure to determine whether $SpO_{2minimum}$ or Td were related to subsequent performance change. $SpO_{2minimum}$ had a moderate negative correlation with performance of the IHT subjects 17 post exposure ($r = -0.31$), such that those subjects that showed less desaturation during the 10-min hypoxic test had better performance improvements, but the correlation between $SpO_{2minimum}$ and performance change 2 days post exposure was trivial ($r = -0.15$). Similar correlations where found between Td and performance change 2 ($r = 0.15$) and 17 days ($r = 0.05$) post-hypoxic exposure.

Exposure Sessions

The placebo group's arterial oxyhaemoglobin saturation during the last minute of the last breathing session of each day remained at normal levels (Figure 2). The IHT group's arterial oxyhaemoglobin saturation decreased significantly from 91.0 ± 7.2% (mean ± between-subject standard deviation of the last 60 sec of the last breathing session of the day) on day 1 to 81.0 ± 6.6% on day 18.

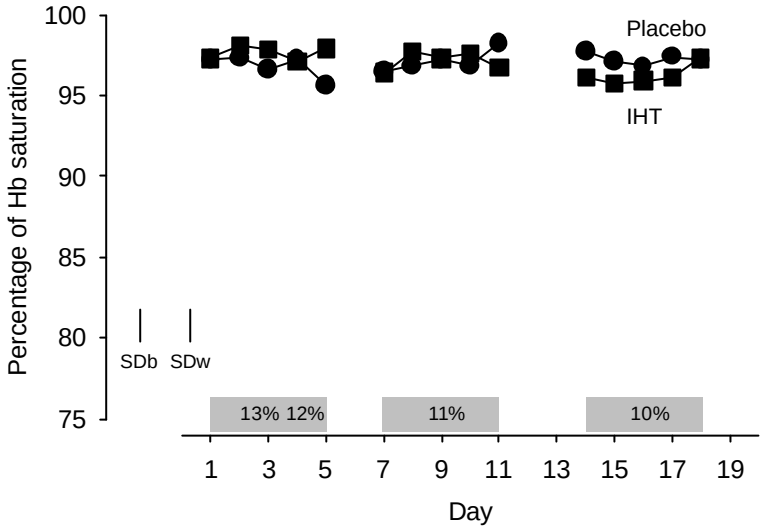
Figure 2. Mean arterial oxyhaemoglobin saturation of the last 5-min breathing session of each day.



Values are the mean of the last minute of the last 5-min hypoxic or placebo breathing session for each day; bars are the standard deviations between subjects (SD_B) and within a subject (SD_W).

By the end of the 5-min recovery breathing sessions the IHT group's arterial oxyhaemoglobin saturation had recovered to be similar to the placebo groups (97.6 ± 0.9% on day 1 and 96.4 ± 4.3% on day 18) (Figure 3).

Figure 3. Mean arterial oxyhaemoglobin saturation of the last recovery breathing session of each day.



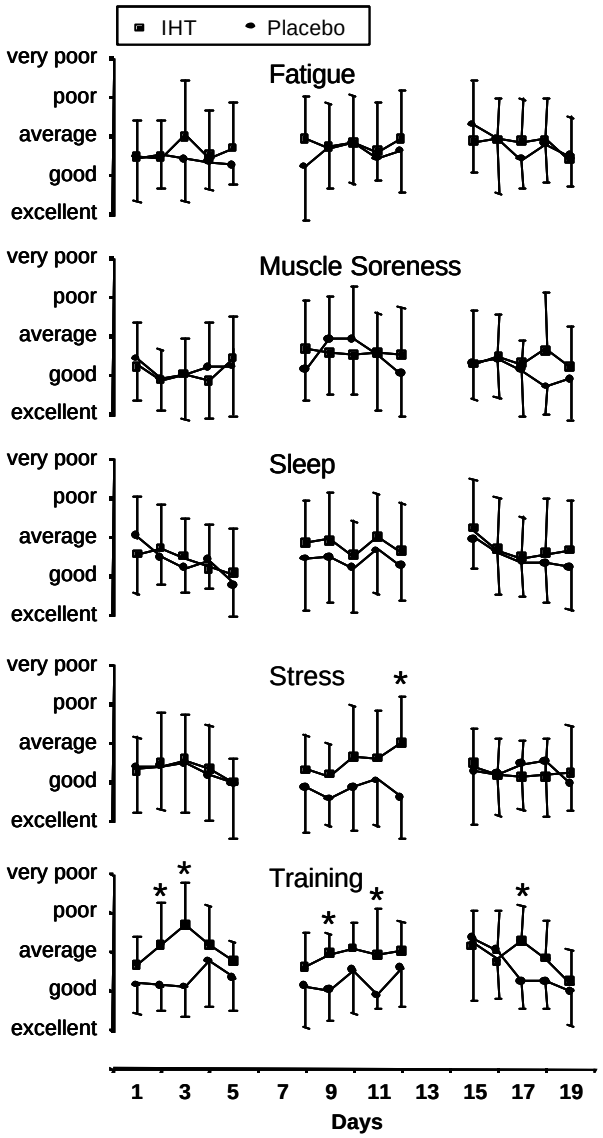
Values are the mean of the last minute of the last 5-min recovery breathing session for each day; bars are the standard deviations between subjects (SD_B) and within a subject (SD_W).

When the IHT group were separated into responders (improvement in performance > 0.5%) and non-responders, a moderate negative correlation was found between arterial oxyhaemoglobin saturation on the last hypoxic session of the last day and performance at 2 (-0.38) and 17 (-0.27) days post hypoxic exposure.

Subjective Effects

On most days subjective ratings of overall stress, fatigue, muscle soreness and sleep were not significantly different between the IHT and placebo groups, however the subjective rating of training stress increased significantly in the IHT group during the first few days of hypoxic exposure and continued to be higher during the second week of the study. By the end of the third week perceived training stress in both groups were again similar (Figure 4).

Figure 4. Subjective rating of fatigue, muscle soreness, sleep, overall stress, and training quality in the IHT and placebo groups during the 3-week study.



Values are the means and between-subject standard deviations; * indicates significant differences between the IHT and placebo groups.

Training Parameters

There was no significant difference in volume of training reported by the two groups during the study period ($p = 0.25 – 0.60$). As most of the subjects were multi-sport endurance athletes the type of training varied considerably from swimming and kayaking through to biking and running and in some instances subjects trained in a number of disciplines in one day.

Table 6. Training duration for the placebo and intermittent hypoxic training groups.

	Placebo	IHT
Training volume ($h.wk^{-1}$)		
week 1	10.2 ± 6.1	7.6 ± 4.2
week 2	9.1 ± 5.8	10.5 ± 6.8
week 3	9.3 ± 7.5	6.6 ± 2.8
3-weekly mean	9.5 ± 7.5	8.2 ± 3.8

Values are the mean ± between-subject standard deviation.

CONCLUSION

This investigation demonstrated that the use of intermittent normobaric hypoxia in 5 minute intervals for 90 minutes a day, 5 days per week for 3 weeks is sufficient to elicit significant and worthwhile improvements in 3-km performance in well-trained subjects. We have also demonstrated that such an IHT protocol can elicit changes in haematological indices that suggest an acceleration of erythropoiesis. However, the 10-min hypoxic test found only a moderate correlation with subsequent performance enhancement, and is probably not a useful test to determine responders to simulated altitude training from non-responders. It is also important to note that while subjects are using IHT their total training stress increases and risks of overtraining and poor performance may develop if not managed appropriately.

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