Influences of Normobaric Hypoxia Training on Metabolic Risk Markers in Human Subjects

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ABSTRACT

HAUFE, S., S. WIESNER, S. ENGELI, F. C. LUFT, and J. JORDAN. Influences of Normobaric Hypoxia Training on Metabolic Risk Markers in Human Subjects. *Med. Sci. Sports Exerc.*, Vol. 40, No. 11, pp. 1939–1944, 2008. **Purpose:** Endurance exercise and hypoxia regulate pathways that are crucial to glucose and lipid metabolism. We hypothesized that training under hypoxia results in similar or even greater metabolic improvement compared with exercise under normoxia at a lower workload. **Methods:** We randomly assigned 20 healthy men to single blind training under hypoxia (FiO_2 = 15%) or normoxia (FiO_2 = 21%). Subjects trained thrice weekly for 60 min over a 4-wk period at a heart rate measured at 3 $mmol \cdot L^{-1}$ lactate during pretraining exercise testing. Before and after the training period, we determined body composition, venous blood parameters, oral glucose tolerance, and blood pressure. Furthermore, we assessed oxygen uptake ($\dot{V}O_2$), lactate, and respiratory quotient, and heart rate (HR) during incremental exercise testing, both in hypoxia and in normoxia. Training workload was 1.39 ± 0.2 $W \cdot kg^{-1}$ in the hypoxia and 1.67 ± 0.15 $W \cdot kg^{-1}$ in the normoxia group ($P < 0.001$) with an identical training heart rate in both groups. **Results:** Exercise capacity improved similarly with both interventions. With hypoxia training, body fat content, triglycerides, HOMA-Index, fasting insulin ($P < 0.05$), and area under the curve for insulin ($P < 0.01$) during the oral glucose tolerance test improved more than with the training in normoxia. We did not observe major changes in adipokine measurements. **Conclusion:** Endurance training in hypoxia over a 4-wk period elicits a similar or even better response in terms of cardiovascular and metabolic risk factors than endurance exercise in normoxia. The fact that workload and, therefore, mechanic strain can be reduced in hypoxia could be particularly beneficial in obese patients and in patients with orthopedic conditions.
Key Words: BODY FAT MASS, GLUCOSE TOLERANCE, ENDURANCE PERFORMANCE, ADIPOKINES

Regular physical activity improves cardiovascular and metabolic risk factors and has been indispensable in prevention programs (15,20). One important question is how training stimuli can be optimized such that obese patients receive a maximal metabolic and cardiovascular benefit while minimizing injury risk. Addition of normobaric hypoxia to endurance exercise is a promising approach (4,11,19). The idea behind this suggestion is that normobaric hypoxia may improve the response to endurance training even though exercise intensity is reduced compared with training under normoxia. Reduction in exercise intensity may minimize the risk for orthopedic injuries. In this event, hypoxia and exercise may have a synergistic effect on muscular and systemic metabolism (25,29). Indeed, both stimuli regulate pathways that are crucial to glucose and lipid metabolism. At the molecular level, hypoxia, as well as exercise, increases hypoxia-inducible factor-1 (HIF-1) production (2,22). The transcription factor HIF-1α targets genes involved in oxygen transport, glycolysis, and glucose transport (32). Regular exercise training increases muscle glycogen storage and glucose tolerance in part through increased GLUT 4 expression (33). Prolonged hypoxia also augments GLUT 4 expression (7). Recently, training under hypoxia was shown to increase peroxisome proliferator-activated receptor gamma coactivator-1α (PGC1α) mRNA expression (35). PGC1α induces mitochondrial biogenesis and plays a key role in the regulation of muscle fatty acid oxidation (12). Possibly, hypoxia in combination with endurance training may have use in prevention programs. Therefore, we conducted a single blind pilot study in healthy subjects to test the hypothesis that training under hypoxia results in similar or even greater improvement in body weight and metabolic risk markers compared with exercise under normoxia.

METHODS

Subjects. We included 20 healthy men who were not on any medications in our study. Men who reported more than two athletic activities per week were excluded. In the

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weeks before and during the study, subjects lived at an altitude of 30–80 m above sea level. Our institutional review board approved the study and written informed consent was obtained before study entry.

Experimental design. We advised subjects to continue their current activity level and lifestyle throughout the study. Two weeks after a basal metabolic evaluation, subjects were subjected to two pretraining incremental exercise tests. One test was conducted in normobaric normoxia [partial pressure of inhaled oxygen (P_IO_2) 150 mm Hg]. Another test was conducted on a separate day in normobaric hypoxia (P_IO_2 103 mm Hg) corresponding to P_IO_2 at 2740 m altitude. Then, subjects were randomized to normoxia (NO) or hypoxia training (HY) in a single blinded fashion. Within 1 wk after completion of the training, anthropometric and metabolic measurements were repeated. Another 3 to 6 d later, subjects underwent posttraining exercise testing.

Metabolic and cardiovascular evaluation. Subjects reported to the laboratory in the morning after an overnight fast. We determined body weight and height in a standardized fashion. Body composition was measured using a multifrequent bio impedance analysis system (BIA 5 series; Denner, Germany), a valid method for estimating body fat when subjects are within a normal body fat range (24). Additionally, we conducted an air displacement plethysmographie (ADP) (BodPod; Life Measurement, Inc., Concord, CA) to assess lean body mass and fat mass. Recently, it has been reported that ADP is a valid method to determine body composition compared with hydrodensitometry, dual-energy x-ray absorptiometry, and the four-comportment model in adults (3,10). After a resting period of at least 5 min, we determined seated blood pressure and heart rate with an automated blood pressure cuff (Dinamap; Critikon, Tampa, FL). Then, we measured oxygen consumption and carbon dioxide production in the supine position over a 40-min period by indirect calorimetry (Deltatrac II; Datex Ohmeda, Duisburg, Germany). We computed resting energy expenditure and respiratory quotient. Afterward, we obtained venous blood samples for determination of fasting insulin, glucose, leptin, total adiponectin, resistin, and retinol-binding protein 4 (RBP4). Finally, subjects underwent oral glucose tolerance testing with blood samples taken at baseline and 15, 30, 45, 60, 90, and 120 min after glucose ingestion to measure glucose and insulin. Glucose and insulin were determined by standard laboratory procedures in a certified clinical chemistry laboratory. Homeostasis model assessment (HOMA) index of insulin resistance was calculated from fasting insulin and glucose data by the following formula: (insulin [$\mu U \cdot mL^{-1}$] $\times$ glucose [$mmol \cdot L^{-1}$])/22.5 (31). Adipokines were determined in the analytical laboratory of Immundiagnostik (Bensheim, Germany) according to the protocols given by the manufacturers with the specified assays: leptin sandwich ELISA (DRG Instruments, Marburg, Germany): intraassay coefficient of variation (CV) 7%, interassay CV 9%; visfatin EIA (ALPCO Diagnostics, Salem, NH): intraassay CV 4%, interassay CV 8%; adiponectin multimeric EIA (ALPCO Diagnostics): intraassay CV 8% for total adiponectin and 10% for HMW adiponectin, interassay CV 14% for total adiponectin and 17% for HMW adiponectin; resistin EIA (Immundiagnostik, Bensheim, Germany): intraassay CV 3%, interassay CV 5%; and RBP4 ELISA (Immundiagnostik): intraassay CV 5%, interassay CV 10%. The preliminary medical evaluation was within 5 d after the end of the training period, with at least 48 h after the last training unit.

Hypoxia room. Exercise testing and training sessions under normoxia and under hypoxia were conducted in a hypoxia room (LOWOXYGEN® Systems GmbH, Germany) with a volume of approximately 100 m^3. Oxygen content within the chamber could be reduced by insufflating nitrogen which was produced from room air through a molecular sieve. Room oxygen and carbon dioxide within the room were continuously monitored by a sensor electrode throughout the test and training sessions.

Exercise testing. Subjects underwent testing at ambient room temperature (21–22°C) approximately 4 h after they had ingested a light breakfast. Incremental exercise tests to exhaustion in normoxia and in hypoxia were conducted in random order, with a resting period of at least 48 h between tests. Tests were conducted on a motorized treadmill (h/p/cosmos mercury 4.0, h/p/cosmos sports & medical gmbh, Germany) with 0% slope. Initial running speed was 2.5 $m \cdot s^{-1}$ and increased every 5 min by 0.3 $m \cdot s^{-1}$, with a pause of 90 s between steps. We monitored brachial blood pressure (Dinamap), oxygen saturation (Nonin Medical Inc., Plymouth, MN), and breath-by-breath gas exchange (Vmax Spectra Model 229D analyzer; SensorMedics, Yorba Linda, CA). At baseline and after each exercise step, we obtained arterialized blood samples from the finger pad to determine blood lactate concentration. Arterialization was achieved by application of hyperemic cream (Finalgon®; Boehringer-Ingelheim, Germany) to the fingertip for 5 min before the test was started. At the same time points, we obtained venous blood parameters from a catheter that was placed in a large antecubital vein.

Training program. Subjects were submitted to a 4-wk training program. They ran on a treadmill 60 $min \cdot d^{-1}$, 3 $d \cdot wk^{-1}$, for 4 wk, either under normoxic or hypoxic conditions. To achieve similar relative exercise intensities in both intervention groups, subjects were trained at a heart rate corresponding to the 3 $mmol \cdot L^{-1}$ lactate value in the F_IO_2-specific incremental test. Treadmills were equipped with a heart rate monitor such that running speed was adjusted automatically to maintain a stable heart rate throughout the training session. We decided to use a treadmill protocol because this resembles daily life activities more than cycling and uses several muscle groups. At a given workload, oxygen consumption tended to be higher with reduced lactate concentrations for running compared with cycling (6). Accordingly, fat oxidation rates at a given

workload were shown to be higher during running than cycling over a wide range of intensities (1).

Statistical analysis and calculations. We evaluated spirometric data at exhaustion and at the individual anaerobic threshold. We applied a specialized lactate software program (Lactware; MED-Tronik GmbH, Germany) to analyze the individual anaerobic threshold. Data were first tested for distribution normality and variance homogeneity. Differences between values obtained pre- and posttraining for a particular group were analyzed using Student's paired *t*-test. To test for both intervention and time (before vs after), we used an ANOVA for repeated measures followed by Student–Newmann–Keuls posttest. Differences were considered to be significant for $P \leq 0.05$. If not otherwise indicated, values are given as mean ± SD.

RESULTS

Ten subjects in each group completed the entire study protocol. Demographic and physiological baseline characteristics for both treatment groups are given in Table 1. Groups were well matched for body composition and age. Moreover, exercise testing results at baseline did not differ between groups. In particular, individual anaerobic thresholds, time to exhaustion, $\dot{V}O_{2peak}$, and lactate measurements at exhaustion were similar in both groups when testing was conducted under normoxic and when testing was conducted under hypoxic conditions. Yet, in both groups, individual anaerobic thresholds, time to exhaustion, and $\dot{V}O_{2peak}$ were lower when testing was conducted under hypoxia. Training workload was 1.39 ± 0.2 W·kg^{-1} in the hypoxia group and 1.67 ± 0.15 W·kg^{-1} in the normoxia group (Fig. 1 top, $P < 0.001$). At these workloads, average training heart rates were 150 ± 5.3 beats·min^{-1} in the hypoxia group and 150 ± 4.6 beats·min^{-1} in the normoxia group (Fig. 1 bottom).

Table 2 shows changes in exercise testing results in the hypoxia and in the normoxia training group. Time to exhaustion improved similarly in both groups, both when testing was conducted in normoxia and when testing was conducted in hypoxia. However, changes in peak $\dot{V}O_2$ were only observed in the hypoxia group during normoxic testing. At the individual anaerobic threshold, lactate ($P < 0.05$) and heart rate were slightly reduced after the training period, both when exercise testing was conducted in normoxia and when testing was conducted in hypoxia. However, these measurements improved similarly with normoxia and with hypoxia training.

TABLE 1. Baseline characteristics.

	Hypoxia Group	Normoxia Group
Number of subjects	10	10
Age, yr	29 ± 5.9	28.1 ± 5.2
Body weight, kg	82.5 ± 12.0	78 ± 7.5
BMI, kg·m^{-2}	25.1 ± 1.9	24 ± 1.6
Height, m	1.8 ± 0.1	1.8 ± 0.1
Blood pressure, mm Hg	122 ± 12/67 ± 8	116 ± 23/68 ± 7
Heart rate, beats·min^{-1}	60 ± 8.9	57 ± 9.4

BMI, body mass index.

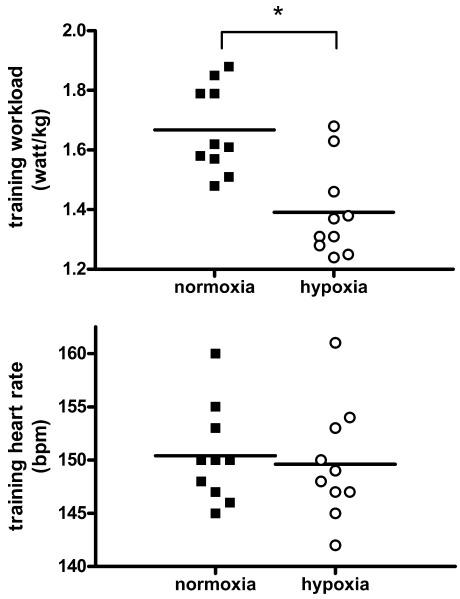

FIGURE 1—Individual data and mean of training workload (*top*) and training heart rate (*bottom*) in subjects randomized to training in normoxia or in hypoxia. *$P < 0.05$.

Figures 2–4 illustrate changes in body weight, body mass index (BMI), body fat, and lipoproteins, as well as insulin and glucose responses to an oral glucose load with hypoxia and with normoxia training. Training in hypoxia caused significant reductions in triglyceride levels ($P < 0.05$), whereas endurance training alone had no such effect. Body weight, BMI, total cholesterol, HDL cholesterol, LDL cholesterol, and blood pressure did not change significantly with either intervention. However, the reduction in body fat mass achieved with training in hypoxia was greater than the reduction observed with training in normoxia (bio impedance analysis $P < 0.05$; ADP $P = 0.072$).

TABLE 2. Exercise testing before and after training.

	Hypoxia Group		Normoxia Group	
	Pre	Post	Pre	Post
Maximal				
$\dot{V}O_{2max}$, mL·min^{-1}·kg^{-1}				
Normoxia	44 ± 6.2	47 ± 5.5	47 ± 3.4	47 ± 4.3
Hypoxia	39 ± 4.4	39 ± 5.9	44 ± 4.6	44 ± 4.8
HR_{max}, beats·min^{-1}				
Normoxia	195 ± 10	189 ± 11	195 ± 6.3	191 ± 8.9
Hypoxia	189 ± 9.9	185 ± 11	192 ± 3.6	188 ± 7.5
Lactate, mmol·L^{-1}				
Normoxia	12 ± 2.6	12 ± 1.9	13 ± 4.5	11 ± 3.7
Hypoxia	12 ± 2.9	11± 2.4	13 ± 3.3	12 ± 3.9
TtE, min:s				
Normoxia	32:16 ± 02:55	35:32 ± 02:24	34:48 ± 02:15	37:13 ± 02:29
Hypoxia	28:01 ± 02:56	29:50 ± 02:34	30:26 ± 02:11	32:32 ± 02:41
Anaerobic threshold				
$\dot{V}O_2$, mL·min^{-1}·kg^{-1}				
Normoxia	36 ± 5	38 ± 4.5*	38 ± 2.9	38 ± 4.6
Hypoxia	34 ± 2.9	34 ± 4.7	36 ± 3.1	36 ± 4.7
HR, beats·min^{-1}				
Normoxia	174 ± 7.5	169 ± 11	173 ± 7.4	172 ± 11
Hypoxia	171 ± 9.5	170 ± 12	172 ± 9.5	173 ± 6.9
Lactate, mmol·L^{-1}				
Normoxia	6.4 ± 1.4	5.5 ± 1.3*	6.3 ± 1.5	5.4 ± 1.4*
Hypoxia	6.8 ± 1.8	5.5 ± 0.9*	6.7 ± 1.4	5.7 ± 1.1*

Pre, before training; Post, after training; $\dot{V}O_2$, oxygen uptake; HR, heart rate; TtE, time to exhaustion, oxygen uptake. *$P < 0.05$ compared with before training.

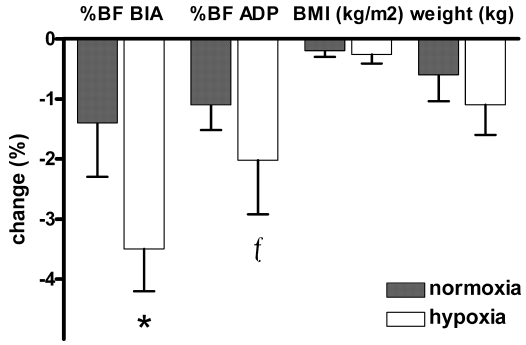

FIGURE 2—Changes in percentage body fat content (%BF) for BIA, ADP, BMI, and body weight in subjects randomized to training in normoxia or in hypoxia. Data are mean ± SEM. *$P < 0.05$, $fP = 0.073$.

Resting energy expenditure in the normoxia group was 1640 ± 156 kcal·24 h^{-1} before and 1657 ± 185 kcal·24 h^{-1} after the training period. In the hypoxia group, resting energy expenditure was 1823 ± 227 and 1702 ± 123 kcal·24 h^{-1} before and after the training, respectively. HOMA index, fasting insulin ($P < 0.05$), and area under the curve for insulin ($P < 0.01$) during the oral glucose tolerance test improved more with training in hypoxia than with training in normoxia. Circulating adipokine concentrations before and after training are given in Table 3. Except for a trend for leptin reduction in both training groups, we did not observe major changes in adipokine measurements.

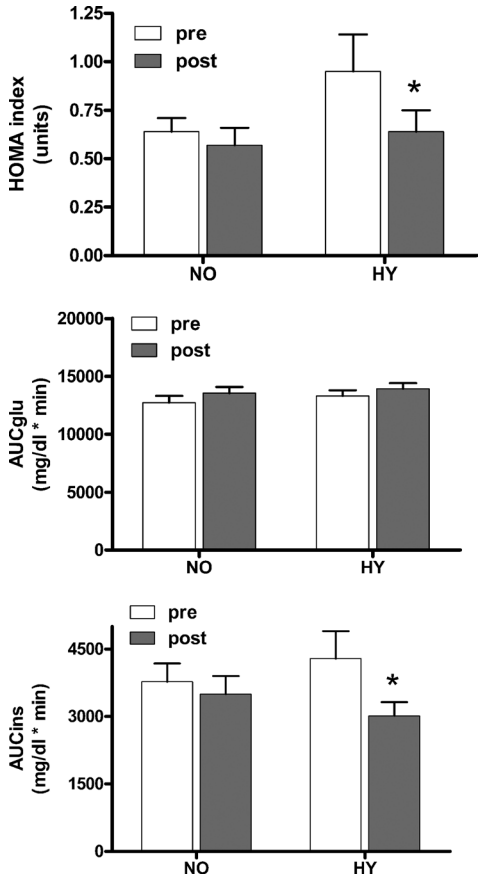

FIGURE 4—Glucose and insulin responses to oral glucose tolerance testing before and after training in normoxia or in hypoxia. Data are mean ± SEM. *$P < 0.05$.

DISCUSSION

The main finding of our study is that over a 4-wk period, endurance training in hypoxia elicits a similar or even better response in terms of cardiovascular and metabolic risk factors than endurance exercise in normoxia. However, training workload was significantly lower with hypoxia training.

Earlier studies suggested that training under moderate hypoxia ("living low to training high") can improve endurance performance in athletes (14,25). An improvement in endurance performance assessed by $\dot{V}O_{2max}$ and time to exhaustion with intermittent hypoxic training was observed in some (11,25,29) but not all studies (8,19). Substrate utilization and maximal oxygen consumption ($\dot{V}O_{2max}$) are tightly coupled to muscular mitochondrial oxidative capacity (5). Moreover, improved aerobic performance is associated with quantitative and qualitative mitochondrial adaptations (26,34). Impaired oxidative capacity and muscular mitochondrial insufficiency contribute to insulin resistance (18,21). However, studies applying training under hypoxia in the clinical setting are rare. In our study, subjects trained at an identical heart rate in hypoxia and in normoxia suggest a comparable cardiovascular training stimulus in both groups. Over a 4-wk period, we did not observe a major additional improvement in endurance performance when subjects trained in hypoxia.

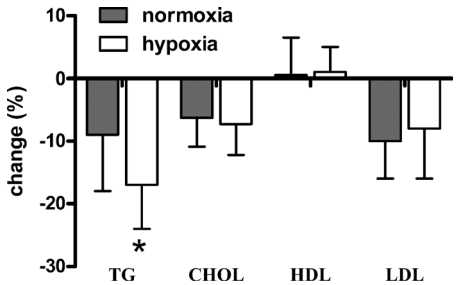

FIGURE 3—Changes in triglycerides (TG), cholesterol (CHOL), HDL, and LDL in subjects randomized to training in normoxia or in hypoxia. Data are mean ± SEM. *$P < 0.05$.

TABLE 3. Adipokine values before and after training.

	Hypoxia Group		Normoxia Group	
	Pre	Post	Pre	Post
Leptin, ng·mL^{-1}	3.9 ± 1	2.3 ± 0.7*	2.3 ± 0.8	1.9 ± 0.6*
Adiponectin, ng·mL^{-1}	4630 ± 450	4110 ± 450	4970 ± 750	4770 ± 710
Resistin, ng·mL^{-1}	0.75 ± 0.2	0.73 ± 0.2	1.09 ± 0.3	1.73 ± 0.7
RBP 4, μg·mL^{-1}	29 ± 2.6	24 ± 2.1	24 ± 2.2	24 ± 3.2

Pre, before training; Post, after training; RBP 4, retinol binding protein 4. *$P = 0.07$ compared with before training.

Previous studies showed a relative increase in glucose oxidation rate during physical activity after hypoxic training (11,14,29). The phenomenon was attributed to transactivation of HIF-1 (32). Activation of the regulatory subunit HIF-1α leads to cellular adaptations, which counteract the effects of reduced oxygen supply to cells under hypoxic conditions. These include induction of several genes, such as those of encoding Phosphofructokinase and GLUT-1 among other proteins involved in glucose metabolism (22,32).We did not determine insulin sensitivity directly. However, we obtained measurements that are highly correlated with insulin sensitivity or resistance including the HOMA index and glucose and insulin responses to oral glucose tolerance testing. In this event, all these measurements improved with training and even more so when training was combined with hypoxia.

The beneficial effect of endurance training on triglyceride levels has been attributed to increased postexercise lipid oxidation (17). Hypoxia also tends to raise lipid oxidation through the transcription coactivator PGC1α (35). By coactivating the peroxisome proliferator activated receptor (PPAR), a family of lipid activated nuclear hormone receptors, PGC1α plays a key role in mediating adaptive regulation of muscle fatty acid oxidation (12). Furthermore, in people living at high altitude, total cholesterol levels, blood pressure, and cardiovascular mortality are surprisingly low (23,30). Decreases in total cholesterol and triglycerides have also been observed with acute exposure to environmental hypoxia (9). Conceivably, combination of exercise and hypoxia may have a greater effect on triglyceride concentrations than each stimulus alone. Our study supports this idea.

Adipokines, such as leptin, adiponectin, resistin, and RBP4, have been implicated in the pathogenesis of metabolic and cardiovascular disease (28). Adiponectin increases muscular fatty acid oxidation and protects against atherosclerotic changes in the vessel wall (27). Resistin is predominantly secreted by macrophages within adipose tissue and appears to inhibit insulin action and promote vessel wall inflammation (13). Some authors described an association of increased levels of RBP4 with measures of insulin resistance (16). Therefore, we reasoned that changes in metabolic and cardiovascular risk factors with training could be related to changes in adipokine production. We observed a mild reduction in circulating leptin levels, which may have been secondary to reduction in adipose tissue mass. Adiponectin, resistin, and RBP did not change.

Our study has several important limitations. The project was designed as a pilot study with a relatively small number of subjects. Therefore, differences in glucose and lipid responses between treatment groups have to be interpreted with caution. Furthermore, we did not assess insulin sensitivity directly. Despite these issues, we suggest that training in hypoxia elicits a similar cardiovascular stimulus at a lower workload. Even though workload is reduced, training in hypoxia elicits a similar or even greater benefit compared with normoxia training in terms of changing cardiovascular and metabolic risk factors. The reduction in workload may reduce the risk for orthopedic injury, which could be particularly beneficial in obese patients and in other patient groups in whom exercise capacity is limited by orthopedic conditions.

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