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Protective effects of exercise training on endothelial dysfunction induced by total sleep deprivation in healthy subjects

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ABSTRACT

Background: Sleep loss is a risk factor for cardiovascular events mediated through endothelial dysfunction.
Aims: To determine if 7 weeks of exercise training can limit cardiovascular dysfunction induced by total sleep deprivation (TSD) in healthy young men.
Methods: 16 subjects were examined during 40-h TSD, both before and after 7 weeks of interval exercise training. Vasodilatation induced by ACh, insulin and heat (42 °C) and pulse wave velocity (PWV), blood pressure and heart rate (HR) were assessed before TSD (controlday), during TSD, and after one night of sleep recovery. Biomarkers of endothelial activation, inflammation, and hormones were measured from morning blood samples.
Results: Before training, ACh-, insulin- and heat-induced vasodilatations were significantly decreased during TSD and recovery as compared with the control day, with no difference after training. Training prevented the decrease of ACh-induced vasodilation related to TSD after sleep recovery, as well as the PWV increase after TSD. A global lowering effect of training was found on HR values during TSD, but not on blood pressure. Training induces the decrease of TNF-α concentration after TSD and prevents the increase of MCP-1 after sleep recovery. Before training, IL-6 concentrations increased. Cortisol and testosterone decreased after TSD as compared with the control day, while insulin and E-selectin increased after sleep recovery. No effect of TSD or training was found on CRP and sICAM-1.
Conclusions: In healthy young men, a moderate to high-intensity interval training is effective at improving aerobic fitness and limiting vascular dysfunction induced by TSD, possibly through pro-inflammatory cytokine responses.(ClinicalTrial:NCT02820649)

1. Introduction

Sleep loss is considered as a risk factor for cardiovascular events and exercise-related injuries that are mediated through endothelial dysfunction, in addition to hormonal and inflammatory responses [1–3]. Endothelial dysfunction is currently recognized as an early key factor in the development of atherosclerosis. Indeed, endothelial dysfunction is associated with numerous risk factors for cardiovascular disease, including hypertension, coronary artery disease, vascular calcifications, heart failure with preserved ejection fraction (HFpEF), sudden death and metabolic syndrome [4,5]. The mechanisms underlying the association between sleep duration and cardiovascular disease remain unclear. In healthy subjects, acute total sleep deprivation (TSD) or sleep restriction are sufficient to trigger endothelial dysfunction [6–10] and to increase arterial stiffness [11]. Endothelial dysfunction was initially suggested to be triggered by factors such as inflammation or increased sympathetic activity. We have previously shown that 40 h of acute TSD can decrease endothelial-dependent and independent cutaneous vascular reactivity, with an increase in the endothelial cell activation biomarker E-selectin [6]. Furthermore, it delayed until after sleep recovery the increase in sICAM-1, IL-6 (a pro-inflammatory cytokine), and norepinephrine (a reliable marker of the increase in sympathetic

Non-standard abbreviations and acronyms: ACh, acetylcholine; BP, blood pressure; CVC, cutaneous vascular conductance; DAP, diastolic arterial pressure; HR, heart rate; HRR, heart rate reserve; ICAM-1, intracellular adhesion molecule-1; IL-6, interleukin-6; IMT, intima media thickness; MAP, mean arterial pressure; MCP-1, monocyte chemoattractant protein-1; Pmax, maximal peak power at exercise; PWV, pulse wave velocity; SAP, systolic arterial pressure; SkBF, skin blood flow; TNF-α, tumor necrosis factor-alpha; TSD, total sleep deprivation; VO_{2max}, maximal oxygen uptake.

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nervous system activity) [6]. Our research group has also demonstrated elevation of the pro-inflammatory cytokine TNF-α concentration, particularly after 34 and 37 h of sleep deprivation [12].

A growing body of evidence has demonstrated that structured exercise programs or lifestyle interventions are effective strategies for reducing cardiovascular risk (NIH Consensus) [13]. Both cross-sectional and longitudinal studies have revealed an improvement in endothelial function in response to exercise training in subjects displaying abnormal baseline endothelial function, including the elderly, young pre-hypertensive subjects, and patients with heart failure or coronary artery disease [14,15]. High-intensity interval training combined with continuous moderate intensity training has emerged as a novel strategy to improve macro- and micro-vascular reactivity as well as glycemic control in type 2 diabetic patients [16,17]. This training program has also been used to improve cardiorespiratory fitness in healthy sedentary men and women [16,18,19]. Moreover, it has been shown that adherence to short-term (four weeks) high-intensity interval training (as compared to moderate intensity training) is greater in individuals with prediabetes [20]. One high-intensity training program (three times per week during twelve weeks) was found to be superior to moderate intensity training with regard to reversal of myocardial remodeling, aerobic capacity, endothelial function, and quality of life in patients with post-infarction heart failure [21]. The beneficial effect of chronic exercise on endothelial function was suggested to increase bioavailability of nitric oxide (NO) through an increased anti-oxidative status and/or anti-inflammatory effect [22,23]. However, the effect of exercise training, regardless of its intensity, on endothelial function in healthy subjects remains not clear. Cross-sectional studies show little effect of exercise training on endothelial function when comparing healthy physically active subjects with inactive subjects, as well as longitudinal exercise training studies of healthy individuals [14,24].

Recent studies and reviews have suggested an interaction between exercise and sleep in which exercise training could protect against the physiological responses induced by sleep deprivation [2,3]. Along these lines, we previously described that 7 weeks of intense exercise training in rats decreases the inflammatory response to TSD in the hippocampus (as a measure of IL-1β mRNA expression and protein content, and TNF-α content) and in plasma (IL-6) [25].

The present work aims to evaluate the effects of 7 weeks of combined moderate and high intensity exercise interval training on endothelial function, and on the inflammatory and hormonal responses in healthy subjects submitted to 40 h of TSD. Assessing endothelial-related changes in cutaneous vascular conductance (CVC) after application of vasoactive drugs, in particular ACh, is considered as a validated, reproducible and non-invasive method [26–29]. So, we hypothesized that exercise training should reduce the altered endothelial-dependent cutaneous vasodilation related to TSD, possibly through inflammatory and hormonal responses.

2. Methods

2.1. Subjects

Sixteen healthy men (27.3 ± 5.4 years old) participated in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, revised in 2001. Informed written consent was obtained from each participant. The Hôtel Dieu – Ile de France 1 (Paris) institutional ethics committee and the *Agence Nationale pour la Sécurité du Médicament* (ANSM) approved the protocol [N°IDRCB: 2014_A01103-44].

All subjects underwent a detailed medical history review and examination. Exclusion criteria included shift workers, smokers, those with daily consumption of alcoholic beverages, those consuming >400 mg of caffeine per day, subjects with a body mass index (BMI) >30 kg/m^2, and those taking medication. Subjects with excessive daytime somnolence (Epworth Sleepiness Scale ≥ 9) [30], sleep complaints (Pittsburgh Sleep Quality Index > 5) [31] or an inability to be considered as an intermediate chronotype on the Horne and Ostberg questionnaire (score < 31 or >69) [32] were also excluded. Subjects were considered as untrained if the Ricci Gagnon questionnaire [33] score was <35 (mean ± SD: 18.4 ± 5.1, range: 11–25) and if they participated in <2 h of sports per week.

2.2. The total sleep deprivation [TSD] protocol (Fig. 1)

Subjects were individually housed in temperature-controlled bedrooms (24 ± 1 °C) for 3 days at the Hôtel-Dieu APHP Hospital (Paris, France). During the first day (Control), subjects were familiarized with the laboratory procedures and equipped for continuous polysomnography. They went to bed at 23:00 and woke up at 07:00. On the next day, TSD began at 07:00 and finished at 23:00 after 40 h of continuous wakefulness. Subjects left the laboratory at 19:00 during the 3rd day, after a recovery night (23:00–07:00). Subjects returned to the laboratory for the same protocol after 7 weeks of physical training. During the TSD protocol, six investigators were systematically present in the laboratory with at least 2 of them with the subjects, and rotations of 12 h were organized in order to maintain a good level of their alertness. When the subjects were about to fall asleep (eyes closed, head down), they were gently and immediately woken up.

Cardiovascular measurements were made following a 10-min stabilization period from 09:00 to 11:00 during the Control day, TSD and recovery. Body mass (in kg) was assessed at 07:45 during the Control day, TSD and recovery, using an electronic balance (SECAse_920; ±0.2 kg). Tricipital and subscapular skin folds were assessed during the Control day using a Holtain Skinfold Caliper (Crymich, UK; mean of five measurements per assay), and umbilical perimeter was measured. The fat mass was calculated using Lohman's formula [34].

During the experiment, polysomnographic variables (comprising 6 electroencephalogram, 2 electrocardiogram, 2 electrooculogram and 2 electromyogram derivations) were continuously monitored (Actiwave®, CamNtech; England) and analyzed offline (Somnologica™; Reykjavik, Iceland).

Subjects were prohibited from exercise, as well as caffeine, tobacco, alcohol, and other psychoactive substances 24 h before and throughout the study. Meals and caloric intake were standardized for all subjects in accordance with the recommendations of the National Health Agency for Security Food, Environment and Labor (ANSES) (2600 kcal/day, providing 55% carbohydrate, 30% fat and 15% protein). For the majority of the population, this is the daily energy intake for men aged between 20 and 40 years under regular daily activities. Water was allowed *ad libitum*.

2.3. Exercise training program (Fig. 1)

Subjects performed three training sessions per week over a 7-week training period (21 sessions) on an ergocycle [19]. Two trained research assistants supervised participants during the training phase. This included per week:

- **One constant intensity session** comprised of a 10 min warm-up (40–50% maximal HRR) followed by 35 min of constant intensity from 50 to 55% (weeks 1 to 5) up to 60–65% (weeks 6 to 7) of the HRR, followed by 10 min of recovery. Heart rate reserve (HRR) is the difference between resting heart rate (HRrest) and maximum heart rate (HRmax) [HRR = HRmax − HRrest] calculated during a maximal cycling incremental test (IET).
- **Two interval training sessions**, with a 20 min constant intensity (45–50% maximal HR) warm-up, followed by 5 blocks of 1 min maximal intensity (95–100% HRR) with a 1.5 min rest recovery between blocks. The number of maximal intensity blocks was progressively increased from 5 blocks (week 1) to 10 blocks (week 7).