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From rest to stressed: endothelin-1 levels in young healthy smokers and non-smokers

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ABSTRACT

Introduction. Endothelin-1 (ET-1) is a potent vasoconstrictor produced by vascular endothelial cells, and a known marker of endothelial dysfunction. However, the acute and chronic effects of smoking and nicotine gum on the ET-1 response to acute physical stress in young healthy smokers have not been investigated.

Methods. Healthy smokers (n = 35) and non-smokers (n = 35) underwent an exercise test to exhaustion (maximal oxygen consumption) on a treadmill. Smokers were assessed a) after 12 h smoking abstinence (termed chronic smoking), b) immediately after smoking one cigarette (termed acute smoking), and c) immediately after chewing nicotine gum. Blood was drawn immediately pre-exercise, and 3 minutes post-exercise. During exercise, cardiorespiratory parameters were obtained breath-by-breath using an automated metabolic cart. Plasma ET-1 levels were quantified using enzyme-linked immunosorbent-assay. The above protocol was designed to incorporate exercise as a vascular stressor to reveal changes that would not be detected at rest.

Results. Mean age was 28.6 ± 7.2 years and body mass index (BMI) was 23.6 ± 3.2 kg/m^2. Post-exercise ET-1 levels were significantly lower than pre-exercise levels in non-smokers ($P < 0.001$) and smokers under all three conditions ($P = 0.005$, $P < 0.001$, $P = 0.001$, respectively). There were no differences in post-exercise ET-1 levels between non-smokers and smokers under all three conditions, however the absolute and relative decrease in ET-1 levels was significantly smaller in chronic smokers compared with non-smokers ($P = 0.007$ and $P = 0.004$). Chronic smokers had a significantly lower exercise-induced change in tidal volume

Abbreviations: BMI, body mass index; CO_2, carbon dioxide; ET-1, endothelin-1; FeO_2, fraction of expired O2; DBP, diastolic blood pressure; $FeCO_2$, fraction of expired CO_2; FiO_2, fraction of inspired O_2; $FiCO_2$, fraction of inspired CO_2; HR, heart rate; IPAQ, international physical activity questionnaire; NO, nitric oxide; O_2, oxygen; Peak METs, peak metabolic equivalents; $PETO_2$, partial pressure of end-tidal O_2; $PETCO_2$, partial pressure of end-tidal CO_2; PIF, peak inspiratory flow; PEF, peak inspiratory flow; PGI_2, prostaglandin; RER, respiratory exchange ratio; RR, respiratory rate; RPM, revolutions per minute; SBP, systolic blood pressure; SD, standard deviation; Ti, inspiratory time; Ttot, total time for a tidal volume cycle; VDA, anatomical dead space; VE, exhaled minute ventilation; VI, inspired minute ventilation; Vt, tidal volume; VO_2, oxygen consumption; VO_{2max}, maximum oxygen consumption.

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($P = 0.050$), fraction of expired CO_2 ($P = 0.021$), oxygen consumption ($P = 0.005$), carbon dioxide elimination ($P = 0.004$) and peak expiratory flow ($P = 0.003$) compared with non-smokers. Furthermore, the decrease in ET-1 observed in non-smokers in response to exercise was significantly associated with exercise induced-changes in inspiratory time, time for a tidal volume cycle, respiratory frequency, inspired minute ventilation and peak inspiratory flow.

Conclusions. An acute decrease of circulating ET-1 in response to acute maximal exercise in young healthy individuals was noted. Chronic smokers had a significantly diminished decrease in ET-1 compared with non-smokers, however there were no significant differences in the ET-1 response between smokers under the three smoking conditions. Smokers were not able to achieve the same exercise-induced changes in cardiorespiratory parameters as non-smokers. By incorporating exercise as a vascular stressor in our study, we have taken a novel approach to provide evidence of an altered ET-1 and cardiorespiratory response that would not otherwise be observed at rest in young active healthy smokers.

1. Introduction

The vascular endothelium, through its release of numerous vasoactive substances, plays a dynamic role in the continuous modulation of vascular tone. Endothelin-1 (ET-1) is fundamental in this capacity, acting as the most potent vasoconstricting peptide [1]. ET-1 is synthesized mainly in vascular endothelial cells through the cleavage of its inactive precursor, big ET-1, resulting in a 21 amino acid peptide that is secreted predominantly abluminally, but also into the circulation [2]. Production of ET-1 is enhanced in response to a number of different stimuli, including hypoxia, tissue injury or stress, and very rapidly exerts its biological effects through binding to ET_A and ET_B receptors. Specifically, the vasoconstricting actions of ET-1 are mediated through the ET_A and ET_B receptors found on vascular smooth muscle cells (VSMCs) [2]. However, ET-1 can also mediate vasodilation by binding to ET_B receptors found on endothelial cells, triggering the release of nitric oxide (NO) and prostaglandins (PGI_2) [3,4]. ET_B receptors also function in the rapid clearance of ET-1 from the circulation mainly within lungs, but also the kidneys [3,4]. A balance between the ET_A- and ET_B-mediated effects of ET-1 is essential to the overall maintenance of endothelial integrity and vascular homeostasis [5].

The dysregulation of ET-1 expression or activity has been shown to contribute to the pathogenesis of several cardiovascular diseases, such as hypertension and atherosclerosis [2,5]. Cigarette smoking is one of the most important risk factors for developing atherosclerosis and cardiovascular events [6], and is known to implicate ET-1 in this process [7]. Nicotine and the many other harmful constituents in cigarette smoke, such as tar, carbon monoxide, metals, and oxidant compounds, have been shown to increase ET-1 mRNA expression in rats [8] as well as plasma ET-1 levels in humans, leading to impaired endothelial dependent vasodilation [9,10]. There is evidence to suggest that both acute cigarette smoking and nicotine consumption alone lead to a rapid elevation of plasma ET-1 in humans [9,11,12].

Circulating ET-1 has been shown to play a key role in regulating vessel tone in the systemic, coronary and pulmonary vasculature during acute exercise to comply with increased oxygen demands. The release of ET-1 during exercise is driven by changes in shear stress within the vessel, hypoxia, and the levels of endogenous factors, such as angiotensin II, norepinephrine and vasopressin [13]. However, the levels of ET-1 in the vasculature during exercise remain intricately controlled by its inhibitor, NO, in order to maintain the necessary balance between vasoconstriction and vasodilation throughout the vasculature for adequate blood flow distribution during exercise [14]. Therefore, exploring the response of ET-1 to acute exercise has the potential to provide critical information about the functioning state of the vascular endothelium.

While North American smoking rates have been on the decline in recent years, young adults still have the highest prevalence of smoking in the United States (17.3% among those aged 18–24 years and 21.6% among those aged 25–44 years) and Canada (20.3% among those aged 20–24, and 21.8% among those aged 25–34), compared to other age groups [15,16]. Although considerable research has been carried out on the long-term cardiovascular consequences of smoking, the extent of the underlying dysfunction in young, physically active, otherwise healthy smokers has not been fully established. Since ET-1 dysregulation may indicate early disturbances of endothelial dysfunction [17], we sought to uncover the response of ET-1 to smoking by using exercise as vascular stressor to reveal changes that would not otherwise be observed at rest in a young, healthy population. Therefore, we aimed to estimate differences in ET-1 levels at rest and after acute exercise among young, active, healthy non-smokers and current smokers. The latter group was examined a) after 12 hours abstinence from smoking (termed chronic smoking), b) immediately after smoking a cigarette (termed acute smoking) and c) immediately after chewing nicotine gum.

2. Methods

2.1. Ethical Approval

The study was approved by the ethics and scientific reviews boards of the McGill University Health Centre (MUHC). Written informed consent was obtained from all subjects, and our study conformed to the standards set by most current version of the Declaration of Helsinki [18].

2.2. Subjects

Recruitment for the study was done through notices on local University and Montreal area websites. Included in the study