

## Clinical Research

# Acute High-Intensity Intermittent Aerobic Exercise Reduces Plasma Angiotensin-Like 2 in Patients With Coronary Artery Disease

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### ABSTRACT

**Background:** Circulating levels of angiotensin-like 2 (ANGPTL2), a proinflammatory and proatherogenic protein, are elevated in patients with coronary artery disease (CAD). We hypothesized that high-intensity intermittent exercise (HIIE), known to be beneficial in patients with CAD, would reduce circulating ANGPTL2 levels.

**Methods:** Plasma levels of ANGPTL2 were measured before and 20 minutes, 24 hours, and 72 hours after an acute exercise session in a crossover study comparing HIIE to moderate-intensity continuous exercise (MICE) in 14 patients with CAD and 20 age-matched and 20 young healthy controls.

**Results:** Pre-exercise ANGPTL2 levels were 3-fold higher in patients with CAD than in age-matched controls ( $P < 0.05$ ) and correlated negatively with  $V_{O_{2max}}$ /lean body mass ( $P < 0.0001$ ). In healthy

### RÉSUMÉ

**Introduction :** Les concentrations circulantes de la protéine angiotensinoïdique-like 2 (ANGPTL2), une protéine pro-inflammatoire et proathérogène, sont élevées chez les patients souffrant de maladie coronarienne (MC). Nous avons posé l'hypothèse que l'exercice par intervalles de haute intensité (EIHI), connu pour être bénéfique chez les patients souffrant de MC, pourrait réduire les concentrations circulantes d'ANGPTL2.

**Méthodes :** Les concentrations plasmatiques d'ANGPTL2 ont été mesurées avant, puis 20 minutes, 24 heures et 72 heures après une séance d'exercice à court terme dans une étude transversale comparant l'EIHI à l'exercice continu d'intensité modérée (ECIM) chez 14 patients souffrant de MC et 20 témoins en santé appariés selon l'âge, ainsi que 20 témoins jeunes et en santé.

Regular physical training is known to decrease all-cause mortality,<sup>1-4</sup> reduce the risk of cardiovascular disease (CVD),<sup>2,3</sup> slow the progression of coronary artery disease (CAD), and improve cognitive function.<sup>2</sup> Globally, regular exercise increases life expectancy, even in patients with CVD.<sup>5,6</sup> Multiple mechanisms appear to underlie the beneficial effects of exercise training: exercise delays the age-related increase in

blood pressure and aortic stiffness,<sup>7</sup> improves the lipid profile and endothelial function,<sup>1-4,8-10</sup> reduces oxidative stress,<sup>10</sup> and promotes an anti-inflammatory effect by lowering the production of proinflammatory cytokines and proteins, such as interleukins, adhesion molecules, fibrinogen, and C-reactive protein (CRP).<sup>1-3,10-13</sup> Thus, the mechanisms of benefit from exercise involve interconnected systems, but the pathways for these effects are not fully understood.

Angiotensin-like 2 (ANGPTL2), a circulating proinflammatory protein belonging to the angiotensin-like family,<sup>14-16</sup> has recently been reported to contribute to chronic inflammation associated with atherosclerosis,<sup>17,18</sup> insulin resistance, and obesity.<sup>19-21</sup> ANGPTL2 is produced by adipocytes,<sup>21</sup> endothelial cells,<sup>17,18,21</sup> and monocytes/macrophages and promotes chronic inflammation.<sup>21</sup> Accordingly, circulating levels of ANGPTL2 are elevated in patients with

Received for publication December 16, 2014. Accepted January 27, 2015.

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controls, ANGPTL2 levels were low and not affected by HIIE or MICE. In patients with CAD, ANGPTL2 levels decreased significantly by 41% after 20 minutes of HIIE, a reduction that was maintained after 24 and 72 hours ( $P < 0.05$ ). In contrast, although ANGPTL2 levels decreased by 47% after 20 minutes of MICE, they increased by 104% after 24 hours and returned to baseline values after 72 hours ( $P < 0.05$ ). A negative correlation was observed between this increase in ANGPTL2 levels and the mean rate-pressure product (heart rate  $\times$  systolic blood pressure; index of myocardial O<sub>2</sub> consumption) measured during MICE, suggesting that subclinical ischemia might promote ANGPTL2 expression.

**Conclusions:** In patients with CAD, circulating ANGPTL2 levels are acutely reduced after HIIE and transiently increased after MICE. A sustained reduction in circulating ANGPTL2 levels could contribute to the chronic beneficial cardiometabolic effects of HIIE in patients with CAD.

CAD,<sup>17,18,20,21</sup> diabetes, insulin resistance, and obesity.<sup>15,19,22</sup> Interestingly, a study performed in overweight but otherwise healthy Japanese men showed that a 3-month lifestyle intervention combining nutritional and physical activity counselling reduced ANGPTL2 plasma levels in parallel with weight loss and an improvement in lipid metabolism.<sup>23</sup> In this latter study, however, the modalities of exercise were not mentioned, and the effect of exercise on ANGPTL2 levels could not be deciphered from the effect of the diet. The effects of physical training on circulating levels of ANGPTL2 in patients with risk factors for CVD have never been reported. We hypothesized that the known beneficial effects of exercise in patients with CAD would be associated with a reduction in circulating ANGPTL2. Our objective was to measure ANGPTL2 levels in patients with CAD before and after acute aerobic exercise; we compared the effects of high-intensity intermittent exercise (HIIE) and isocaloric moderate-intensity continuous exercise (MICE)—2 approaches with known beneficial effects in patients with CVD.<sup>24-26</sup>

## Methods

### Participants

In the context of a crossover study comparing HIIE with MICE, fit patients with stable CAD ( $n = 13$  men and 1 woman), fit age-matched healthy controls ( $n = 10$ men and 10 women), and fit young healthy controls ( $n = 10$ men and 10 women) who provided written informed consent were recruited at the cardiovascular prevention center of the Montreal Heart Institute. Blood samples from patients with CAD were obtained from 14 of 19 patients included in a previous study in which inclusion and exclusion criteria have been described.<sup>27</sup> Young and older healthy controls were recruited starting in January 2012, and the study protocol was registered at [controlled-trials.com/ISRCTN46169845](http://controlled-trials.com/ISRCTN46169845). Controls were

**Résultats :** Les concentrations d'ANGPTL2 avant l'exercice étaient 3 fois plus élevées chez les patients souffrant de MC que chez les témoins appariés selon l'âge ( $P < 0,05$ ) et corrélaient négativement avec le  $VO_{2max}$ /la masse maigre ( $P < 0,0001$ ). Chez les témoins en santé, les concentrations d'ANGPTL2 étaient faibles et non affectées par l'EIHI ou l'ECIM. Chez les patients souffrant de MC, les concentrations d'ANGPTL2 diminuaient significativement de 41 % après 20 minutes d'EIHI, une réduction qui était maintenue après 24 heures et 72 heures ( $P < 0,05$ ). En revanche, bien que les concentrations d'ANGPTL2 diminuaient de 47 % après 20 minutes d'ECIM, elles augmentaient de 104 % après 24 heures et revenaient aux valeurs initiales après 72 heures ( $P < 0,05$ ). Une corrélation négative était observée entre cette augmentation dans les concentrations d'ANGPTL2 et le produit moyen de la fréquence et de la pression (fréquence cardiaque  $\times$  pression artérielle systolique; indice de consommation du myocarde en O<sub>2</sub>) mesuré durant l'ECIM, ce qui montre que l'ischémie sous-clinique favoriserait l'expression d'ANGPTL2.

**Conclusions :** Chez les patients souffrant de MC, les concentrations circulantes d'ANGPTL2 sont réduites à court terme après l'EIHI et augmentées de manière transitoire après l'ECIM. Une réduction soutenue des concentrations circulantes d'ANGPTL2 pourrait contribuer aux effets cardiométaboliques bénéfiques à long terme de l'EIHI chez les patients souffrant de MC.

without cardiovascular, pulmonary, or muscular diseases and without cardiovascular risk factors. Patients with CAD had hypertension (3 of 14 [21%]), diabetes (2 of 14 [14%]), and dyslipidemia (11 of 14 [79%]), were obese (3 of 14 [21%]) and had a family history of CVD (7 of 14 [50%]), but were non-smokers and trained regularly on a voluntary basis at the cardiovascular prevention center. Baseline characteristics of all participants are presented in Table 1. The research protocol was approved by the Research Ethics and New Technology Development Committee of the Montreal Heart Institute.

### Experimental design

On the first visit, patients and healthy controls underwent a complete medical evaluation and a maximal continuous graded exercise test, which allowed the measurement of anthropometric parameters, maximal oxygen uptake ( $VO_{2max}$ ,  $mL \cdot min^{-1} \cdot kg^{-1}$  of lean body mass), blood pressure, and heart rate.<sup>28</sup> During 2 subsequent weeks, all participants performed in random order the 2 isocaloric exercise sessions (HIIE and MICE) under the supervision of an exercise physiologist, a nurse, and a cardiologist.<sup>28</sup> All tests were conducted on an electromechanically braked bicycle ergometer; all experimental details concerning the exercise sessions have been previously described.<sup>28</sup> Briefly, HIIE consisted of a 10-minute warm-up and 2 10-minute blocks of intermittent exercise (15 seconds at 100% of maximal aerobic power/15 seconds of passive recovery) separated by a 4-minute passive recovery. MICE duration was 28 minutes at 70% maximal aerobic power. Exercise sessions were randomly performed within a 1-week interval.

### Laboratory analyses

Venous blood samples were collected 4 times for each exercise session (10 minutes before and 20 minutes, 24 hours, and 72 hours after exercise) and centrifuged, and plasma was stored at  $-80^{\circ}C$ . Nonfasting circulating levels of ANGPTL2 were

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