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Effect of strenuous exercise on mediators of inflammation in patients with coronary artery disease

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ABSTRACT

Background: Coronary artery disease (CAD) is considered a low-grade inflammatory disease. We aimed to identify effects of short-term strenuous exercise on mediators of systemic inflammation, endothelial and platelet activation in patients with angiographically verified CAD. We hypothesized that a more pronounced inflammatory response would be present in patients with CAD than in those without CAD.

Methods: In subjects with symptoms indicative of stable CAD, an exercise stress test on a bicycle ergometer was performed. Venous blood samples, taken at rest and within 5 min after end of exercise, were analyzed for the following markers by ELISAs: TNF-α, IL-6, MCP-1, ICAM-1, VCAM-1, E-selectin, P-selectin, CD40L and RANTES. All participants underwent conventional coronary angiography. CAD was defined as having any degree of atherosclerosis.

Results: A total of 110 patients were included, of whom 74 were found to have CAD. Mean exercise duration was 10:06 ± 3:56 min with no significant difference between the two groups. All measured markers changed significantly during exercise ($p \leq 0.012$). A significantly less pronounced increase in CD40L in the CAD group than in the no CAD group was observed ($p = 0.050$), however, after adjustment for hematocrit this difference was no longer significant.

Conclusion: An instant inflammatory response was observed during short-term strenuous exercise in patients with symptoms of CAD. However, the exercise mediated response was not more pronounced in patients with CAD.

1. Introduction

Atherosclerosis is the main underlying process causing coronary artery disease (CAD). In the early phase, atherosclerosis is characterized by accumulation and modification of low density lipoproteins and leukocyte recruitment to the intima of the vascular wall, contributing to endothelial dysfunction and inflammation [1].

Tumor necrosis factor-α (TNF-α), produced by activated inflammatory cells in the atherosclerotic lesion, induces the production of Interleukin-6 (IL-6) which initiates hepatocyte production of C-reactive protein (CRP), one of the most studied biomarkers in this field. TNF-α also seems to induce platelet release of soluble P-selectin and CD40 ligand (sCD40L), which may promote adhesion of circulating monocytes to the vascular endothelium. sCD40L also binds directly to the endothelium, inducing chemokine release and expression of adhesion molecules, such as vascular adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), E-selectin and P-selectin on endothelium. Adhesion molecules further stimulate expression of chemotactic agents such as monocyte chemoattractant protein-1 (MCP-1) in endothelial cells and RANTES (regulated on activation normal T-cell expressed and secreted), released by platelets and other inflammatory cells [2].

This orchestration of inflammatory signaling contributes to further recruitment of immune cells to the site of lesion as well as generating a continuous expression and release of pro-inflammatory molecules, leading to a chronic low-grade inflammatory state, both locally and in

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the general circulation.

Several of these signaling molecules can be quantified in circulating blood and have been shown to be elevated in patients with coronary atherosclerosis [3–6].

In atherosclerotic arteries, a trigger of physical or psychological stress may lead to activation of dysfunctional endothelium with subsequent platelet activation to elicit an acute coronary event. It has been shown that regular exercise, in the long-term, is beneficial for reducing progression of vascular chronic inflammatory states such as CAD, by improving endothelial function [7,8]. In contrast acute vigorous exercise has been reported to provide a more pronounced increase in inflammatory biomarkers reflecting general inflammation, platelet and endothelial activation during exercise, especially in sedentary individuals [9–11]. Regular exercise may have numerous beneficial health aspects, however acute strenuous exercise may cause an acute ischemic cardiac event [12]. The increased stress of vascular endothelium and platelet activation secondary to adrenergic responses occurring during exercise might trigger such an event [13,14].

Dysfunctional endothelium is thought to be more sensitive to the shear stress occurring with acute exercise with a subsequent release of chemoattractant substances and other cytoregulatory factors from activated immune cells and platelets. Triggering of this inflammatory response, may be a pathophysiological explanation behind coronary events during heavy physical load [15]. Till now, clinical studies on the effect of acute exercise on inflammation in CAD patients have shown conflicting results and tend to include very small numbers of participants [16,17].

We aimed to identify effects of short-term strenuous exercise on mediators of systemic inflammation and endothelial and platelet activation in patients with angiographically verified CAD. As CAD is known to be a chronic inflammatory disease and that acute exercise may trigger an acute coronary syndrome, our hypothesis was that an instant increase in factors reflecting pro-inflammatory responses would be more pronounced in patients with CAD compared to patients without CAD.

2. Materials and methods

2.1. Study population

Patients referred for exercise testing due to symptoms suggestive of stable CAD were enrolled in the on-going CADENCE study (clinicaltrials.gov NCT01495091) at the outpatient clinic at Department of Cardiology, Oslo University Hospital Ullevaal, Oslo Norway. Eligible patients were those ≥18 years of age, with symptoms suspected of CAD and intermediate or high risk (Morise risk score ≥9 points) [18]. Exclusion criteria were the following: acute coronary syndrome, clinical heart failure, on-going arrhythmia or implanted pacemaker, moderate to severe valvular heart disease, renal insufficiency (S-creatinine > 150 μmol/L), inability to perform exercise testing or coronary angiography.

All participants have given written informed consent to participate. The study has been conducted in accordance with the Declaration of Helsinki, and the Regional Ethics Committee in South Eastern Health Region in Norway approved the protocol.

A thorough medical history was recorded before inclusion. Prior to exercise testing a physical examination including blood pressure, weight and waist circumference was performed. Hypertension and hyperlipidemia were defined according to known diagnosis or use of specific medication.

The present investigation includes the first 120 patients enrolled in the CADENCE study.

2.2. Exercise stress test

Exercise testing was performed using an electrical bicycle ergometer, monitored by a physician and nursing staff. Registration of a resting 12-lead ECG was performed before exercise, while continuous 12-lead ECG monitoring using a computerized electrocardiogram was used during the test. According to protocol the initial workload was 30 W (W) for women and 50 W for men, with a gradual increase of 10 W per minute and participant maintaining a pedaling rate (cadence) of about 65 rotations per minute. Every third minute auscultatory blood pressure was measured and patients were asked about their perceived exhaustion using Borg scale [19]. The exercise test results were assessed by one physician and 10% of the test results were controlled by another physician with 100% concordance of the results. Patients were exercised to exhaustion, if there were no clinical signs of ischemia developed prior to reaching high intensity level. The test was stopped after a recovery time of 5 min. A positive test result was defined as having ST-segment elevation, horizontal or down-sloping ST-segment > 1.0 mm (0.1 mV) at 60 ms after the J point and/or chest pain or discomfort. Reasons for terminating the test were development of suspected pathological ECG changes such as ST-segment elevation, ST-segment depression in leads without Q waves, arrhythmias increasing through exercise, chest pain, patients desire to stop the test and insufficient chronotrope response to exercise, insufficient or exaggerated hypertensive response (systolic blood pressure ≥250 mmHg or diastolic blood pressure ≥115 mmHg).

2.3. Coronary angiography

All study participants were referred to coronary angiography, performed using the standard Seldinger technique, mostly by using radial artery access.

For the purpose of this present investigation CAD was defined as any degree of angiographically verified atherosclerosis, i.e. coronary angiographies described by the operator as having from minimal atherosclerotic changes to significant stenosis.

2.4. Blood samples and laboratory methods

Blood samples were collected prior to exercise at rest and within 5 min after terminating workload, while patients were still seated on the bicycle ergometer, as previously described [20]. At both occasions serum was prepared within one hour by centrifugation 2000*g* for 10 min at room temperature, whereas blood for citrated plasma and EDTA plasma were kept on ice until 30 min before centrifugation 2500*g* at 4 °C 20 min. Markers of general inflammation were assessed by circulating levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1), endothelial and platelet activation assessed by intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, P-selectin, CD40 ligand (CD40L) and regulated on activation normal T-cell expressed and secreted (RANTES). C-reactive protein (CRP) was additionally measured.

TNF-α, IL-6, ICAM-1, VCAM-1, E-selectin and CRP were measured in serum, while P-selectin and MCP-1 were measured in citrated plasma and CD40L and RANTES were measured in EDTA plasma, the latters to avoid release from platelets during coagulation. Commercial ELISAs were used throughout, and except for CRP which was determined by DRG instruments, Marburg, Germany, kits from R&D Systems Europe (Abingdon Oxon, UK) were used, all according to the manufacturers instructions. Inter assay coefficients of variation (CV) in our laboratory were 8.8%, < 5%, 6.6%, 5.3%, 5.2%, < 5%, 7.2%, 4.0%, 5.3% and 12.0% respectively, for the above mentioned markers. According to the manufacturer the sensitivity was 0.10 pg/mL, 0.04 pg/mL, 0.1 ng/mL, 0.6 ng/mL, 0.01 ng/mL, 0.10 mg/L, < 0.5 ng/mL, < 5 pg/mL, 4.2 pg/mL, and 2 pg/mL, respectively.