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Research paper

Isoprostanes as markers for muscle aging in older athletes

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Abstract

Introduction: Production of isoprostanes (IsoPs) is enhanced after acute, intense, and prolonged exercise, in untrained subjects. This effect is greater in older subjects. The present study aims to delineate the profile of acute-exercise-induced IsoPs levels in young and older endurance-trained subjects.

Methods: All included subjects were male, young (n = 6; 29 yrs ± 5.7) or older (n = 6; 63.7 yrs ± 2.3), and competitors. The kinetics of F_2-IsoPs in blood-sera was assessed at rest, for the maximal aerobic exercise power (MAP) corresponding to the cardio-respiratory fitness index and after a 30-min recovery period.

Results: No significant time effect on F_2-IsoPs kinetics was identified in young subjects. However, in older athletes, F_2-IsoPs blood-concentrations at the MAP were higher than at rest, whereas these blood-concentrations did not differ between rest and after the 30-min recovery period.

Conclusion: Because plasma glutathione (GSH) promotes the formation of some F_2-IsoPs, we suggest that the surprising decrease in F_2-IsoPs levels in older subjects would be caused by decreased GSH under major ROS production in older subjects. We argue that the assessment F_2-IsoPs in plasma as biomarkers of the aging process should be challenged by exercise to improve the assessment of the functional response against reactive oxygen species in older subjects.

Keywords: Isoprostanes; Aging; Exercise; Training

1. Introduction

The number of people aged >60 years is expected to double by 2050 (more than 1 in 5 people will be aged >60 years), according to a new report released by the World Health Organization [1]. The phenotypes of the aging process are heterogeneous: some older people will have a level of functionality similar to middle-aged people whereas others will require assistance for daily tasks. Loss of skeletal mass and function, termed "sarcopenia", is one of the most notable

Abbreviations: ROS, reactive-oxygen species; IsoP, Isoprostane; $\dot{V}O_2$max, Maximal oxygen uptake; MAP, Maximal aerobic power; La_{max}, Venous blood-lactate concentration at $\dot{V}O_2$max; La_{30}, Venous blood-lactate concentration at 30 min after exercise; BHT, Butylated hydroxytoluene; MS, Mass spectrometry; HPLC, High-performance liquid chromatography; FSHD, Facioscapulohumeral dystrophy; Nrf2, Erythroid 2-like factor 2; GSH, Glutathione.

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changes during aging and can greatly affect physical performance [2].

In a recent review for the SPRINTT (Sarcopenia & Physical fRailty IN older people: multi-component Treatment strategies) consortium, Calvani et al. reminded us that impaired physical performance, when related to sarcopenia, is associated with a physically frail phenotype, and is a predictor for major negative outcomes [3]. This review supports the need to develop biomarkers to detect and help prevent frailty and sarcopenia. This strategy needs to assess the physiopathological processes and their corresponding biomarkers associated with an impaired muscular function in older subjects. These biomarkers should then be added to a clinical and usual assessment process of frailty in elderly patients.

Oxidative stress is a key biological mechanism that contributes to functional decline during aging [4]. More reactive-oxygen species (ROS) are produced from the mitochondrial respiratory chain, which is known to functionally decline with age [5], but of interest is the associated level of antioxidant activity that may not match age-related oxidant activity. An imbalance between antioxidant and oxidant activity can lead to oxidative molecular damage, defined as "oxidative stress", and is associated with an impaired functional phenotype. This association has been recently supported in an epidemiological study that reported the results from stepwise models fitted from the Framingham Offspring Study. According to these models, biomarkers of oxidative stress were associated with greater frailty and slower gait speeds amongst patients aged $\geq$60 years [6]. Oxidative stress forms the central dogma for "the free-radical theory of aging" [7]. New strategies are needed to assess oxidative stress and to implement multivariate methodologies to screen older subjects and reduce aged-related functional impairment, sarcopenia, and frailty [3,8]. As previously suggested, oxidative stress the defined as a biomarker of the aging process could then be a part of the clinical and usual assessment process of the functional status of elderly patients.

Isoprostanes (IsoPs) are a class of oxidation products. Most IsoPs are produced by ROS that catalyze the peroxidation of polyunsaturated fatty acids. Measurement of IsoPs is considered an accurate way to assess oxidative stress *in vivo* and can be correlated with numerous diseases [9–11]. In healthy and young subjects, acute, intense, and prolonged exercise increases plasma IsoPs levels, which then negatively influences the properties of the skeletal contractile muscles, whereas chronic exercise is associated with a decrease in plasma IsoPs [12–14]. The effect of acute exercise on plasma IsoPs is greater among older adults compared to young subjects [15,16], but fit older subjects can also reduce the generation of oxidative stress compared to unfit older subjects [17]. However, whether endurance-trained older subjects are less prone than endurance-trained younger subjects to counteract the acute-exercise-induced production of IsoPs remains to be determined. This question addresses the physiology of longevity, i.e., whether endurance training in older subjects can restore a "young anti-oxidative" performance level or simply counteracts the effects of aging on ROS production and oxidative stress? The present study aims to delineate the profile of acute-exercise-induced IsoPs levels in young and older endurance-trained subjects (i.e., master athletes aged $\geq$60 years).

2. Methods

2.1. Study design

This study was defined as being exploratory and aimed to delineate data that could support a comparative designed study. This biochemical study was designed to assess the interest of the addition of a biological biomarker assessment during a daily medical-care routines exercise testing feature. Time points for biological assessment were the defined in respect to the plan of this daily clinical-care plan.

2.2. Subjects

As a part of our daily medical-care routines regarding testing of exercise functionality, young and older subjects involved in sport often request a maximal-exercise test to delineate their physiological adaptations to endurance exercise. This request is voluntary.

All the subjects included within this study were sporting competitors. Whilst most young competitors daily tested in our laboratory included both males and females, most of the included subgroup of older athletes (aged $\geq$60 years) were male. All competitors in this study were involved in endurance exercise, with the majority being cyclists. In order to match young and older trained subjects, we prospectively selected young and older male athletes involved in endurance cycling training for competitions. None of the subjects suffered from any medical disease that could have excluded them from intense exercise.

2.3. Clinical examination, exercise testing and blood sampling

All the subjects were assessed for weight and height to define a body mass index (BMI, kg/m^2). Percentage body fat was estimated using the skin-fold method (8 skin folds were measured).

Maximal exercise testing was requested by the subjects to implement their exercise-training program. As a part of the physiological indicators for metabolic responses to endurance exercise, the following were assessed: maximal oxygen uptake ($\dot{V}O_2$max, L.min^{-1}, mL.min^{-1}.kg^{-1}), its corresponding power (maximal aerobic power, MAP, watts), and venous blood-lactate concentration during exercise (one sample was measured at $\dot{V}O_2$max, La_{max}) and at 30 min after (La_{30}).

According to the usual protocols for exercise testing, a maximal graded exercise test was conducted in our laboratory. Subjects used their own bicycle and equipment. Power output was assessed using a Power Tap mobile cycling ergometer® (Cycle Ops, Madison, WI, USA). During the test, oxygen consumption ($\dot{V}O_2$) was assessed using an Oxycon Pro-ergo-spirometer® (Erich Jaeger, Viasys Healthcare, Germany).