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Research Article

CARDIORESPIRATORY FITNESS IS ASSOCIATED WITH C - REACTIVE PROTEIN AS A PRO-INFLAMMATORY CYTOKINE IN ASTHMA PATIENTS

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ABSTRACT
It is widely accepted that asthma is associated with systemic inflammation. This study aimed to analyze whether cardiorespiratory fitness is associated with C-reactive protein (CRP) in adult men with asthma. Venous blood was obtained at rest between 8:00 and 9:00 am in order to measuring serum CRP in twenty men with mild to moderate asthma. Participants were non-athletes, non-smokers and non-alcoholics. The diagnosis of asthma was made by spirometry test. VO2max (mL kg-1 min-1) was measured according to YMCA instrument on bicycle ergometer. Pearson correlations were used to establish the relationship between variables. P value of <0.05 was accepted as significant. Fasting serum CRP concentrations showed strong negative correlation with VO2max ($p = 0.001$, $r = 0.58$). Based on this data, it is concluded that cardiorespiratory fitness is associated with systemic inflammation in asthma patients.

Keywords: *Cardiorespiratory Fitness, Asthma, Inflammation*

INTRODUCTION
Although lung diseases can be prevented to some extent by identifying the risk factors, each year, 6.4 million people die worldwide due these diseases, 80 percent of them in developing countries (Castro-Rodríguez, 2007). Asthma is a respiratory tract disease with allergic origin, which physiologically appears with narrowing of the respiratory airways (Armstrong *et al.,* 2000). Reduced ventilatory reserve, reduced muscle activity, and some respiratory limitations make the disease more severe. The resistance of respiratory tracts in these patients is a key destructive factor in the body's levels of fitness or cardiorespiratory fitness which affects both aerobic and anaerobic fitness (Counil *et al.,* 2006). Hence, the decrease in VO2max, as a measure of cardiorespiratory fitness, in these patients compared to healthy subjects has been reported previously by some studies (Alioglu *et al.,* 2007).
Research findings not only support the role of local inflammation but also the systemic inflammation in asthmatic patients (Sood *et al.,* 2008). It is well known that systemic inflammation plays an important role in allergic and respiratory diseases. Systemic inflammation may also be a factor in the association between respiratory impairments and cardiovascular disease. Decline in respiratory function associated with systemic inflammation as a result of certain plasma proteins has been reported (Kony *et al.,* 2004; Mendall *et al.,* 2000). In this context, some studies have reported an increase in serum or plasma of C - reactive protein (CRP) in patients compared with healthy subjects (Jousilahti *et al.,* 2002; Ford, 2005). CRP is shown to be one of the most important diagnostic factors of inflammatory processes, and measuring and recording it can be a useful tool to diagnose and assess and treat inflammation (Tall, 2004). Some researchers have noted that CRP, as a systemic inflammatory factor, is important in the relationship between asthma and obesity (Butland *et al.,* 2008). As mentioned before, asthmatic patients suffer from both reduced cardiorespiratory fitness and increased CRP levels compared to healthy subjects. Although the relationship between these two factors has frequently been studied in a number of other diseases (Kullo *et al.,* 2007; Naidoo *et al.,* 2012), few studies determined the relationship between them in asthmatic patients. For example, in one study, a direct correlation between VO2max with CRP and fibrinogen in men without symptoms of coronary disease was observed (Kullo *et al.,* 2007). A relationship between VO2max and CRP has also been reported in obese African children (Naidoo *et al.,*

2012). However, this relationship has not been reported in asthmatic patients and hence, the relationship between them can be investigated in these patients.

MATERIALS AND METHODS

Methods

Study Subjects and Recruitment

Subjects was twenty seven sedentary, non-trained adult men with mild to moderate asthma aged 38.6 ± 3.9 year and body mass index 30.5 ± 2.85 kg/m2 were recruited through an accessible sampling for participating in study. Asthma diagnosis and its severity were determined by FEV1/FVC. The study protocol was approved by Ethics Committee of Islamic Azad University, Iran.

All subjects were on asthma with mild to moderate of intensity at least for 3 years. Participants were non-athletes, non-smokers and non-alcoholics. Participants were included if they had not been involved in regular physical activity in the previous 6 months. Subjects with a history or clinical evidence of recent myocardial infarction, coronary artery disease; tobacco use; use of systemic steroids, diabetes treatments and active liver or kidney disease were excluded.

All patients underwent anthropometrical measurements, a resting spirometry testing and fasting blood sampling for measuring serum CRP.

Anthropometric Measurements

All anthropometric measurements were made by the same trained general physician. Body weight and height were measured on the same day to the nearest 0.1 kg and the nearest 0.1 cm, respectively. Percentage body fat was measured using body composition monitor (OMRON, Finland). The Body Mass index (BMI) was calculated using the formula body weight/height2 in terms of kg/m².

After introduction and awareness of the subjects of the objectives of the study and once they had completed consent forms, the process of test implementation began.

Laboratory Assays

In each patient, after control measurements of venous blood sampling and spirometry, a standard level of cycle ergometry test was performed. Venous blood samples were obtained at rest between 8:00 and 9:00 am from the antecubital vein and Serum separated by centrifugation. Blood was drawn after 12 h of fasting and 1 day of minimal physical activity. The Intra- assay coefficient of variation and sensitivity of the method were 8.3% and 10 pg/mL, respectively for CRP.

For spirometry, Subjects were instructed to take maximum inspiration and blow into the pre-vent pneumotach as rapidly, forcefully and completely as possible for a minimum of 6 seconds, followed by full and rapid inspiration to complete the flow volume loop. Subjects were asked to refrain from tea, coffee, chocolates and caffeinated soft-drinks on the day of recording Spirometry. The best of the three trials was considered for data analysis. Cardiorespiratory fitness was assessed as VO2max (mL kg-1 min-1) was measured using a bicycle ergometer in a stepwise fashion according to YMCA instrucment (Mullis *et al.*, 1999).

Statistical Methods

Data were analyzed by computer using the Statistical Package for Social Sciences (SPSS) for Windows, version 11.5. All data were tested for normal distribution by the Kolmogorov-Smirnov test.

The bivariate associations between cardiovascular fitness with serum CRP concentration and other variables were examined with the Pearson rank correlation analysis.

A p-value less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Results

In method section, it was stated that this study aimed to determine the relationship between serum CRP and VO2max in studied patients. In addition, the relation of mentioned variables was also determined with some anthropometrical markers. Body weight, blood chemistry parameters and VO2max are shown in Table 1. All values are reported as mean and standard deviation.

Table 1: Anthropometric and physiological and biochemical characteristics of the study participants

	Minimum	Maximum	Mean	Std. Deviation
VO2max (ml/kg/min)	21	53	35.93	9.219
Age (year)	32	48	38.56	3.906
Height (cm)	171	176	173.74	1.655
Weight (kg)	80	111	92.15	9.097
Body mass index (kg/m2)	26.42	37.09	30.5133	2.85311
Body fat percentage	25.9	36.8	30.111	2.9977
IgE	155	572	339.52	119.327
C-Reactive protein (ng/ml)	260	8680	2463.26	2508.624
FVC	70	94	85.33	6.872
FEV1	61	87	75.56	6.040
FEV1/FVC	65	72	68.93	1.838
Peak expiratory flow	58	99	77.48	13.503
Expiratory vital capacity	74	100	88.48	7.192
Maximal voluntary ventilation	25	35	30.27	2.465

Data by Pearson correlation coefficient test showed that serum CRP is negatively correlated with VO2max ($p = 0.001$, $r = 0.58$, Figure1). A significant negative correlation was also found between VO2max and body weight in study patients $p = 0.001$, $r = 0.62$, Figure2). Maximal oxygen consumption was also negatively correlated with body fat percentage ($p = 0.001$, $r = 0.55$, Figure 4).
Serum CRP concentrations were positively correlated with body weight ($p = 0.000$, $r = 0.71$, Figure 3) and body fat percentage ($p = 0.000$, $r = 0.72$, Figure 5).

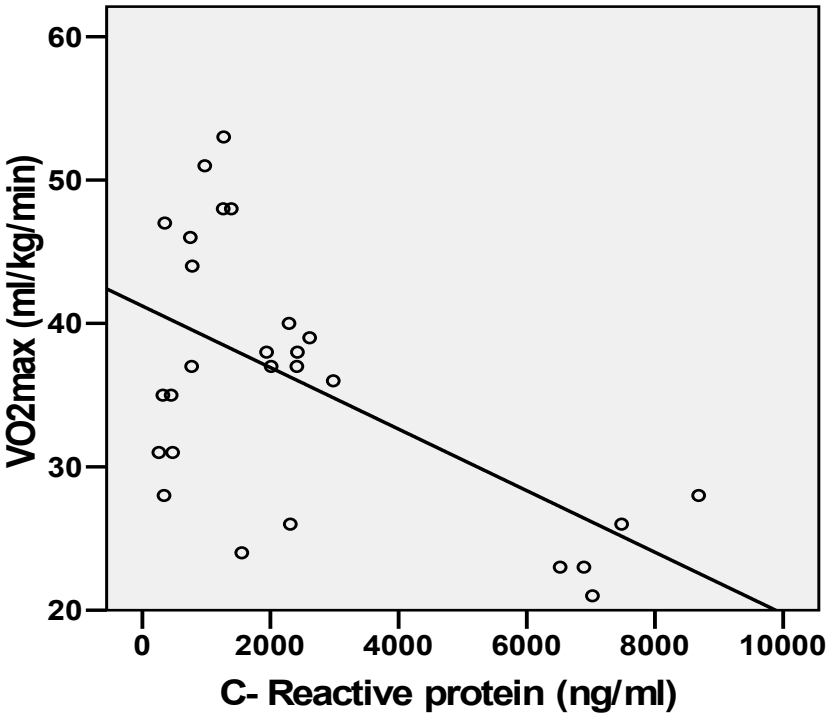

Figure1: Negative significant correlation between serum CRP and VO2mas in asthma patients

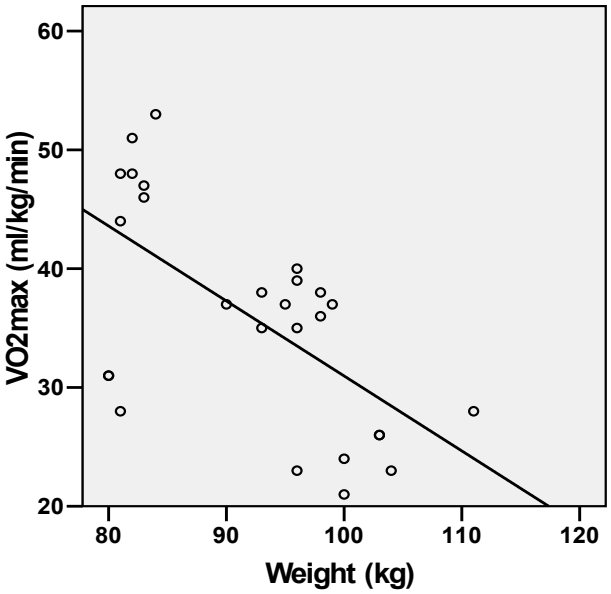

Figure 2: Negative significant correlation between body weight and VO2mas in asthma patients.

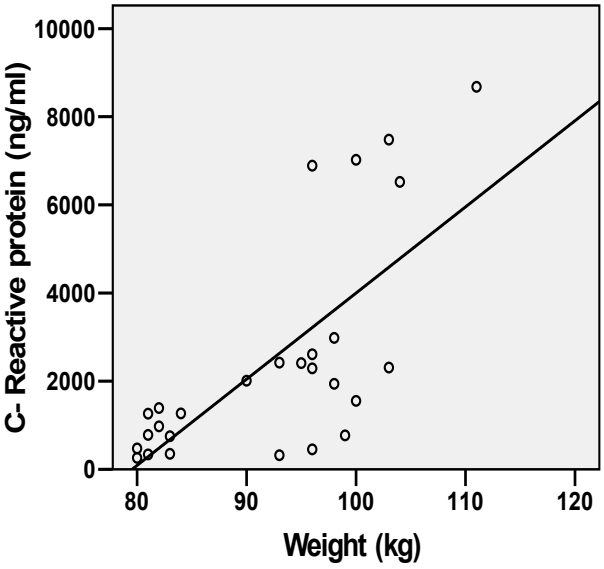

Figure 3: Positive significant correlation between body weight and serum CRP in asthma patients.

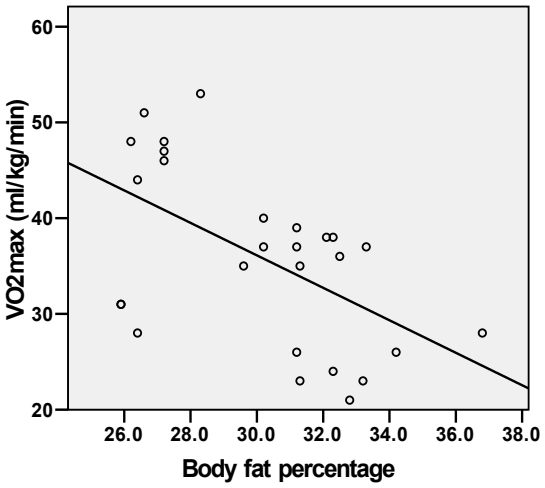

Figure 4: Negative significant correlation between body fat percentage and VO2max in asthma patients

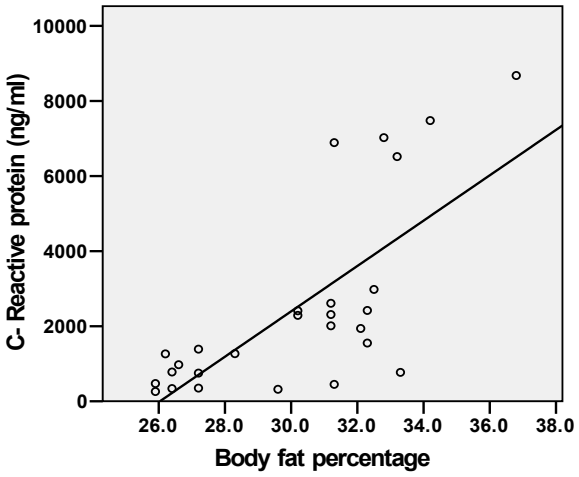

Figure 5: Positive significant correlation between body fat percentage serum CRP in asthma patients

Discussion

Many previous studies have reported that long-term exercise increases cardiorespiratory fitness in healthy or patient populations (Fanelli *et al.,* 2007; Ramazanoglu *et al.,* 1985; Van Veldhoven *et al.,* 2001). On the other hand, the literature has also repeatedly noted the improvement inflammatory profile or reduction in inflammatory cytokine in obese or patient populations (Aggarwal, 2003; Jung *et al.,* 2008; Aldhahi *et al.,* 2003), however some inconsistent findings are also present (Lindgärde *et al.,* 2011). Based on these statements, it can be concluded that improvements in cardiorespiratory fitness are associated with reduced inflammatory cytokine, so that some previous studies have reported the highest levels of cardio-respiratory fitness are associated with lower levels of inflammatory markers (Kullo *et al.,* 2007). Regarding inverse relationship between inflammatory markers with cardiorespiratory fitness, the findings of this study showed a significant inverse relationship between levels of CRP, as an inflammatory cytokine, with cardiorespiratory fitness VO2max, as an indicator, in men with mild to moderate asthma. The findings of the present study are somehow in agreement with the results of some studies that reported a significant reduction in inflammatory cytokine, particularly CRP, following long-term training programs (Shore *et al.,* 2005).

The involvement of inflammatory cytokines in many chronic diseases has been addressed repeatedly. Among the cytokine, CRP has been reported to be one of the most important diagnostic factor in inflammatory processes. Recording and this factor is a convenient tool to detect and evaluate the initial inflammation and its treatment (Tall, 2004). This inflammatory cytokine is one of the prognostic factors of cardiovascular diseases and inflammatory diseases such as asthma, which is negatively, correlated with lung performance indices in these patients (Torres *et al.,* 2006). Literature has noted that the increased secretion of IL-6 in patients with asthma leads to increased secretion of CRP (Broekhuizen *et al.,* 2006). It is well known that CRP levels increases during infection and diseases or disorders of the immune system (Szalai, 2004). Some researchers have noted that the CRP, as a systemic inflammatory factor, is important in the association between asthma and obesity (Butland *et al.,* 2008). In recent years, relatively sufficient evidence of the important role of CRP measurement as an evaluation method for the detection of inflammation in patients with asthma has been provided (Takemura *et al.,* 2006; Fujita *et al.,* 2007). The difference between the levels of this inflammatory cytokines have not much been studied in atopic subjects or respiratory disease patients such as asthma patients compared to less healthy populations. Close relationship between variations in CRP levels and lung capacity, such as FEV1, has already been reported in some studies (Kony *et al.,* 2004; O'Connor *et al.,* 1995; Rijcken *et al.,* 1995) It is known that

the relationship between CRP and respiratory performance in asthmatic patients is similar to the relationship between pulmonary performance and other immune system markers that have been reported in other studies (Amina *et al.,* 2010). However, recent studies suggest a close relationship between elevated CRP and asthma (Jousilahti *et al.,* 2002; Ford, 2005), respiratory damages (Cirillo *et al.,* 2002; Danesh *et al.,* 2004), and over response of bronchus (Kony *et al.,* 2004). Some studies also suggest obesity as a bridge between the Asthma and CRP (Visser *et al.,* 1999; Yudkin *et al.,* 1999). The findings of a recent study showed that adults with asthma have higher levels of CRP compared to healthy subjects (Ford, 2005). In addition to the other findings, an inverse relationship between serum CRP levels and spirometric indices, as well as the positive relationship between this inflammatory cytokines and white blood cells in patients with asthma has also been reported in other studies (Olafsdottir *et al.,* 2005). However, some studies have denied any relationship between CRP levels and spirometric indices such as FEV1, IgE, or the number of white blood cells in this disease (Ebrahim *et al.,* 2012).

Our findings are consistent with some previous studies about the significant inverse relationship between CRP and VO2max as a decisive indicator of cardiorespiratory fitness in other populations of patient. For example, some previous studies have shown that inflammatory markers such as CRP, fibrinogen, and white blood cell count have a significant inverse correlation with cardio-respiratory fitness (Rahimi *et al.,* 2005; Williams *et al.,* 2005). But whether, like CRP, other biomarkers involved in the inflammatory profile, such as other cytokines, are associated with cardiorespiratory fitness is unknown. However, some studies also indicated no relationship between CRP and other inflammatory or anti-inflammatory cytokines such as IL-1ß and IL-10 with VO2max in overweight children (Utsal *et al.,* 2013).

As an overall conclusion, although the findings of this study support a significant negative relationship between CRP and VO2max in asthmatic patients, that does not mean that the changes in this variable in this patients is a kind of causal connection. However, it may be concluded that these two variables affect each other's level directly or indirectly through affecting other hormonal or psychological mediators in asthmatic patients.

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