Effects of interval training on inflammatory biomarkers in patients with ischemic heart failure

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Abstract

Objectives. Exercise training has been proposed to have anti-inflammatory effects. We examined whether aerobic interval training (AIT) can attenuate the inflammatory response in ischemic heart failure (HF) as measured by serum biomarkers representing a broad spectrum of activated inflammatory pathways.

Design. We conducted a controlled prospective trial recruiting 30 patients (19 in the AIT group and 11 in the control group) with ischemic HF and an implantable cardioverter defibrillator (ICD). This study is a sub study of the previously reported "Aerobic interval training in patients with heart failure and an ICD" (Eur J Prev Cardiol. Mar 22, 2015; 22:296-303).

Patients in the AIT group exercised for 12-weeks completing a total of 36 AIT sessions. We analyzed serum levels of C-reactive protein, pentraxin-3, osteoprotegerin, brain natriuretic peptide, neopterin, and soluble tumor necrois factor type 1 and 2, all known to predict an adverse outcome in HF, at baseline and following the 12-week AIT intervention.

Results. The AIT group significantly increased peak oxygen uptake and improved endothelial function compared to the sedentary control group. No statistically significant changes in serum levels of the biomarkers were detected from baseline following the AIT intervention and there were no significant differences in changes in these mediators between the AIT and the control group.

Conclusions. A 12-week AIT intervention, although improving exercise capacity and endothelial function, did not attenuate serum inflammatory biomarkers in stable ischemic HF patients with an ICD on optimal medical therapy.

Introduction

Following a myocardial infarction (MI), there is a complex interplay of various genetic, neurohormonal, inflammatory and biochemical alterations that leads to the clinical syndrome known as heart failure (HF). Numerous immune mechanisms play a role in this process by modulating interstitial fibrosis, causing cardiomyocyte apoptosis and hypertrophy. Since the detection of elevated levels of tumor necrosis factor (TNF) in HF in 1990 [1], different blood derived compounds referred to as inflammatory mediators or biomarkers have received considerable attention. Several of these markers, e.g. high sensitivity C-reactive protein (hs-CRP)[2], pentraxin-3 (PTX3)[3], osteoprotegerin (OPG)[4], soluble TNF receptors (TNF-R1/R2) [5,6], brain natriuretic peptide (BNP)[7], and neopterin [8,9], have demonstrated the ability to predict adverse outcomes like mortality and morbidity in the setting of HF. Some of these biomarkers have also demonstrated the ability to predict new onset HF in presumably healthy individuals (e.g. TNF.R1/R2[10]) or predict cardiovascular death and HF development following acute coronary syndrome (e.g. OPG[11]).

Due to the beneficial effects on mortality, morbidity, exercise tolerance and quality of life, exercise training (ET) is now incorporated into all major HF treatment guidelines (class of recommendation 1/level of evidence A)[12,13]. Despite diverging data, some studies have suggested that ET may be an effective way to attenuate low-grade chronic inflammation [14-16], implicated in the pathogenesis of HF. Recent publications have demonstrated that the more intensive aerobic interval training (AIT) modality might be particularly effective in increasing aerobic fitness and possibly reverse maladaptive cardiac remodeling [17-19] in HF, compared to traditional ET. This beneficial effect of

AIT could potentially reflect a more potent anti-inflammatory effect of this intensive training modality, but these issues are far from clear.

The inflammatory biomarkers hs-CRP, belonging to pentraxin family, [20], OPG, a member of the TNF superfamily [4], PTX3, another member of the pentraxin family that in contrast to CRP also is produced at the site of inflammation including in the vascular bed [3], neopterin, as a marker of monocyte/macrophage activation [8,9], and the TNF-R1 and TNF-R2, as downstream markers of inflammation, [5,6]have all shown to be of prognostic value in patients with HF. In the current trial we evaluated the impact of a 12-week AIT program on patients with ischemic HF and an implantable cardioverter defibrillator (ICD) on these inflammatory markers, representing a broad spectrum of inflammatory pathways that are activated during HF. Our aim was to elicit whether AIT might attenuate inflammatory responses, focusing on biomarkers associated with an adverse outcome in HF.

Methods

Study design

We conducted a prospective, controlled, single-centre study. We have previously reported data on feasibility and effects of the AIT program in a mixed etiology HF ICD population, detailing the design of the AIT intervention[21]. In the current study 30 ICD patients with ischemic HF were enrolled, 19 in the AIT group and 11 in the control group. Figure 1 outlines a flowchart detailing screening and enrolment in the studies.

Patients

Following implantation of an ICD or a cardiac resynchronization therapy defibrillator (CRT-D) at the Department of Cardiology, Stavanger University Hospital, patients were screened for participation in the study. Some studies have shown diverging results on biomarker response depending on HF etiology [16,22]. We therefore only included patients with ischemic HF in this study focusing on biomarker response to AIT. Inclusion criteria were left ventricular ejection fraction (LVEF) <40%. Eligible patients were aged 18 years or above. Exclusion criteria included significant valvular heart disease, inability to give informed consent, inability to participate in regular training due to serious comorbidity or planned surgery within the next three months. The AIT study was controlled, but not randomized, and all patients had to be able to exercise in order to fulfill inclusion criteria. After accepting the request to participate in the AIT study as either a sedentary control or active participant (not knowing if they would be in ET or control group), patients were allocated to control or AIT group. The selection was based on the possibility to attend the (single) outpatient cardiac rehabilitation facility 3 x weekly. The reasons for joining the control group were typically: living distance from rehabilitation centre considered too long to commute, no driver's license or poor public transportation connection between rehabilitation facility and home address. Following device implantation patients were observed for at least two months on stable medical theraphy before entry into the study to allow for initial device adjustments.

Aerobic interval training intervention

Physical therapists specialized in cardiac rehabilitation supervised the AIT. Exercise sessions lasted 60 minutes, three times weekly over a 12-week period. The AIT was conducted in training groups of up to ten individuals. Each session started with 15 minutes of warm-up at 60-70% of maximal heart rate (HR). The patients then

performed four 4-minute intervals at 85% of maximal HR (Borg scale 15-17 Rate of Perceived Exertion (RPE)). Participants exercised by means of a cycle ergometer or by running on a treadmill. The intervals were interrupted by short periods of active recovery at 60-70% of maximal HR lasting 3 minutes. Twenty minutes of cool down and stretching concluded each session. Participants exercised with HR monitors to allow for intensity guidance (Polar RS100, Polar electro, Kempele, Finland).

Cardiopulmonary exercise testing

At baseline and again at 12 weeks the subjects performed a maximal cardiopulmonary exercise test (CPET). The aims were to screen for potential ischemia, calculate the target HR for training intensity and to measure peak oxygen uptake level (VO_{2peak}). Tests were done on an upright, electrically braked cycle ergometer (Model KEM III, Mijnhardt, S.V.Bunnik, The Netherlands) using a 20 watts/minute ramp protocol. The patients were asked to exercise until exhaustion. Gas exchange data were collected continuously with an automated breath-by-breath system (System 2001, medical Graphics Corporation, St.Paul, Minn., USA).

Assessment of endothelial function

Endothelium-dependent and -independent dilation of the brachial artery was measured at baseline and repeated following the intervention at week 12. A single operator (PSM) imaged the brachial artery above the antecubital fossa of the non-dominant arm with the patient in a supine position using a 12-MHz ultrasound Doppler probe (Vivid 7 System; GE Vingmed Ultrasound, Horten, Norway) according to the guidelines by Corretti et al [23]. In a long axis view of the brachial artery a segment with good intimal interfaces between lumen and intima was selected for diameter measurement.

Endothelium-dependent FMD was based on a flow-stimulus after arterial occlusion using cuff inflation on the forearm of at least 50 mm Hg above systolic blood pressure. Endothelium-independent vasodilation was recorded after administration of 0,4 mg Nitroglycerine spray. Images were stored digitally and independently analyzed by two investigators blinded for patient data. Each investigator measured diameters at least three times and reported the average. Reported measurements were the average of the two investigators measurements. Disagreement of the investigators of a FMD of >1% was resolved by reanalysis and consensus. Intra and inter-observer variability of percent FMD in 20 randomly selected patients were previously assessed as 0.69 and 0,94%, respectively.

Inflammatory biomarkers

Blood sampling was performed in the fasting state between 7 and 9 AM from the antecubital vein. Following peripheral venepuncture serum was left to clot in room temperature for approximately 1 hour, and then centrifuged at 2000g at 4° C for 15 minutes, before being stored in aliquots at -80° C. EDTA plasma was immediately centrifuged at 2000g at 4° C for 15 minutes and stored as described above.

The serum levels of CRP, OPG, PTX3, TNF-R1, and TNF-R2 were assessed using DuoSet enzyme immunoassays (EIAs) from R&D Systems (Minneapolis, MN, USA). Neopterin levels were measured using EIA kits from Brahms GmbH (Henningsdorf, Germany). Levels of BNP were analysed from EDTA plasma using the Architect BNP assay on the Architect i2000 SR, Abbott Diagnostics Division (Illinois, Il, USA). The intra- and inter coefficient of variation was <10% for all assays.

Ethics

The study was conducted in accordance with the Declaration of Helsinki, written informed consent was obtained from all participants and the regional ethical review board approved the study. ClinicalTrials.gov: identifier NCT01038960.

Statistical analysis

Data analyses were performed by SPSS version 20.0 (IBM Corp., Armonk, NY). Normally distributed continuous data are expressed as mean with standard deviation (SD) unless otherwise stated. Skewed data are expressed as median with interquartile range. Categorical variables are expressed as frequencies and percentage.

Comparisons between groups were analysed by two-sided t-test or Mann-Whitney U-test, depending on normality of distribution. The Wilcoxon Signed Rank Test was used to compare related samples. Comparisons of categorical variables were generated by the Pearson chi-square test or Fisher`s exact test. All tests were 2-tailed and a p-value below the 0.05 level was considered significant. We performed a post-hoc power analysis, which revealed that a sample size of 19 will discover a large effect (denoted as 0.8) on inflammatory markers with a power of 80%. A sample size of 11 is able to detect a large effect with a power of 58%.

Results

A total of 30 patients completed the study, 19 in the AIT group and 11 in the control group. As displayed in table 1, the groups were matched without any statistically significant differences with respect to the baseline parameters.

Effects of the aerobic interval training intervention

Following the exercise intervention, an increase in peak oxygen uptake (ml/kg/min) from 17.6 to 18.7 (p=0.02) was seen in the AIT group only (table 2). We also noted an increase in maximal ergometer cycle workload from 136.6 watts (W) to 146.3 W following the program in the AIT group (p=0.004).

Regarding endothelial function, we found an improvement in flow-mediated brachial artery reactivity in the AIT group only (table 2).

Effects of AIT program on inflammatory biomarkers

Table 3 displays the numeric values of the inflammatory biomarkers at baseline and following the intervention at 12-weeks. At baseline no difference was noted between the groups. There was, however, a trend for a reduction of PTX3 in the AIT group (p=0.08) (table 3). Following the AIT intervention we did not see any noteworthy change in biomarker serum levels from baseline, neither within groups nor between groups.

Effects of AIT program on natriuretic peptides

Following the AIT intervention there was a non-significant decrease of BNP from a median value of 140.7 pg/mL to 107.4 pg/mL (p=0.09) in the training group, while in the control group median BNP level remained virtually unchanged (128.9 pg/ml to 128.7 pg/ml, p=0.31). However, there was no difference in changes between the two study groups (P=0.37).

Discussion

Despite the AIT intervention having an effect on aerobic fitness and endothelial function, we noted in the present study of patients with ischemic HF and an implantable

9

cardioverter defibrillator (ICD) no effects on serum inflammatory biomarkers that are reported to be associated with an adverse outcome in HF patients.

The assessed biomarkers in this study have all been linked with adverse outcomes in the setting of HF. Both OPG[4] and PTX3[3,23] have displayed prognostic value in the setting of HF, as they are associated with the incidence of death independently of conventional risk factors. Regarding PTX3, although high levels were associated with all cause and cardiac mortality in HF, a pharmacological intervention with the statin Rosuvastatin actually led to an increase in PTX3 levels while hs-CRP levels, another pentraxin, declined[3]. In fact, whether the pro or anti-inflammatory effects of PTX3 dominate in HF is still debated[24]. A Japanese study found that ET decreased plasma PTX3 but not CRP among patients with cardiovascular disease[25]. Our findings similarly showed no effect on hs-CRP while a trend towards a decrease in PTX3 level after the AIT intervention was seen. With regard to ET effects on OPG we have been unable to find studies on HF patients apart from the present. Recent studies on patients with metabolic syndrome[26], obesity[27] and impaired glucose tolerance[28] have reported conflicting findings.

Elevated levels of hs-CRP [20], NP[8,9], TNF and the soluble receptors TNF-R1 and TNF-R2 [29] have also been linked to adverse outcomes in HF. In the same manner as with PTX3 and OPG, we did not detect any decrease in the levels of these biomarkers following AIT. In particular TNF and its soluble receptors (TNF-R1 and TNF-R2) have been extensively studied with respect to HF, and are believed to play a central role in the pathophysiology of HF progression[30]. Among the potential end organ effects of TNF activation are stimulation of myocyte hypertrophy and ventricular remodeling through

effects on extracellular matrix[31]. Also, both neurohormonal activation trough the renin-angiotensin-aldosterone system, as well as beta-adrenergic stimulation via the sympathetic nervous system is able to stimulate TNF activation in the setting of HF[32,33]. Early studies on TNF and its receptors that were positive with regard to an ET effect, were conducted prior to routine use of β-blocking drugs and aldosterone antagonists in HF[14,15]. This may have impacted baseline levels of inflammation in the different study populations to a varying degree and could also have influenced the response to ET. Later studies exploring the effects of ET on inflammation in HF have largely been negative[34-36]. Maybe our population of well compensated, revascularized and optimally medically treated ischemic HF patients do not display enough baseline inflammatory activity to detect an effect of ET. This is also reflected through the relatively low baseline levels of BNP observed in our HF population.

Our negative findings with regard to the AIT intervention on inflammatory biomarkers are in line with newly reported results from a sub-study of the HF-ACTION trial[35]. In this large randomized trial including 928 HF patients, no effect of an ET program on the biomarkers hs-CRP, pro-BNP and cTnT was observed. Controlling for volume of exercise did not alter the findings in the study. The HF action trial has been criticized for not applying a sufficient exercise stimulus, since the predefined target increase in peak oxygen uptake was not met. In our trial, despite a significant effect on aerobic fitness using a high intensity AIT program, we confirm the findings of no impact on levels of biomarkers. Our findings are also consistent with previous trials using AIT as the exercise modality. A small study on HF patients by Wisløff et al. demonstrated a remarkable effect of AIT on cardiorespiratory fitness, endothelial function and reverse LV remodelling, but no effect on hs-CRP[17]. The recently published multicentre trial

SMARTEX HF, comparing AIT to MCT in the HF population did not prove superiority of AIT over MCT regarding aerobic fitness[19]. Similarly, another Norwegian AIT study found no impact on CRP, TNF or NT-pro BNP in a HF population[22]. In the present study we extend these findings by examining a wide spectrum of mediators reflecting distinct as well as overlapping inflammatory pathways. In addition, some of the biomarkers (i.e., OPG and PTX3) have not previously been examined with regard to AIT in a HF population.

The major limitation of this study is the relatively small sample size, hence larger studies are needed to confirm our results.

Conclusion

Among patients with stable ischemic HF, a 12-week AIT program did not affect serum levels of biomarkers representing a wide spectrum of inflammatory pathways. Our findings are largely in line with results from several other studies. There is still a lack of cohesive evidence that can ascribe or link positive benefits of exercise training to an anti-inflammatory effect.

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