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Does group-based high-intensity aerobic interval training improve the inflammatory status in patients with chronic heart failure? A randomized controlled trial.

Running Title: Effects of group-based interventions in cellular adhesion molecules in chronic heart failure.

Short title: The inflammatory status of patients with chronic heart failure.

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ABSTRACT

BACKGROUND: Chronic heart failure (CHF) is a multifaceted syndrome associated with endothelial dysfunction and increased inflammation. Despite the existing controversies regarding the appropriate training modality, it is widely accepted that supervised cardiac rehabilitation (CR) interventions lead to pro-inflammatory biomarkers reduction and cellular adhesion molecules in patients with CHF.

AIM: To quantify the effects of 12-week group-based high-intensity aerobic interval training (HIAIT)/modified group-based HIAIT intervention (m-Ullevaal) vs. moderate continuous training (MICT) on serum levels of pro-inflammatory biomarkers.

DESIGN: Single-blind, two-arm, prospective randomized controlled trial conducted on CHF outpatients performing group-based CR interventions throughout a 12-week period.

SETTING: Medical Center of Outpatient Rehabilitation and Sport Medicine, Plovdiv, Bulgaria.

POPULATION: A total of 120 outpatients of both genders, mean age of 63.73 ± 6.68 years, with stable CHF (NYHA classes II to IIIB, were randomly assigned to HIAIT/ m-Ullevaal (N. = 60) or to MICT (N. = 60) group.

METHODS: Functional exercise capacity (FEC) of the eligible subjects was evaluated through 6-minute walk test (6MWT) and peak oxygen uptake. Blood samples were drawn at baseline, after 12 weeks follow-up for analyses of C-reactive protein (CRP), tumor necrosis factor-α (TNFα) and cellular adhesion molecules (CAM).

RESULTS: Significant decreases in the serum levels of CRP ($P = 0.029$), TNF-α ($P = 0.036$), and vascular cell adhesion molecule-1 (VCAM-1) ($P = 0.040$), were observed after 48 training sessions in the group-based HIAIT/m-Ullevaal intervention, except for intercellular adhesion molecule-1 (ICAM-1), which was higher in the MICT ($P = 0.034$). FEC was significantly inversely related to CRP ($r = -0.72$, $p < 0.05$), and the levels of VCAM-1 ($r = -0.68$, $P< 0.05$).

CONCLUSIONS: Both group-based CR interventions (HIAIT/m-Ullevaal and MICT) significantly reduced the serum levels of CRP, TNF- α, ICAM-1 and VCAM in patients with CHF. However, selected pro-inflammatory biomarkers changes and CAMs favorably decreased in the group-based HIAIT/m-Ullevaal intervention. The responses on serum levels of pro-inflammatory biomarkers and CAMs are dependent upon the type, intensity, and CR intervention duration.

CLINICAL REHABILITATION IMPACT: The group-based high-intensity aerobic interval training reduces significantly the pro-inflammatory biomarkers and cellular adhesion molecules in patients with chronic heart failure.

Key words: Chronic heart failure, adhesion molecules, inflammation, group-based interventions

Introduction

Chronic heart failure (CHF) remains a major public health problem in developed countries despite great advances in pharmacotherapy and exercise-based treatment modalities.[1,2] CHF is a complex clinical syndrome affecting not only the cardiovascular system, but also the humoral, neuroendocrine, renal, and musculoskeletal systems.[3] Earlier studies show an overexpression of pro-inflammatory biomarkers (C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and cell adhesion molecules (CAM) in patients with CHF.[4,5] Both inflammation and endothelial dysfunction are key features of CHF as they contribute to the impaired functional exercise capacity (FEC).[6-8] Increased plasma levels of CAM—intercellular adhesion molecule-ICAM and vascular cell adhesion molecule-VCAM—in patients with CHF correlate with CHF severity,[9] conversely, the elevated high-sensitive CRP in patients with CHF and left ventricular ejection fraction (LVEF) ≤ 50% is considered as an independent prognostic biomarker.[10,11] Exercise-based interventions can improve the circulating levels of selected pro-inflammatory biomarkers such as CRP, TNF-α, and CAMs on pro-inflammatory biomarkers in patients with CHF.[12-15] Although improvements in inflammatory biomarkers are associated with improved FEC,[16,17] results have been inconsistent.[18]

Exercise-based cardiac rehabilitation (CR) is the cornerstone of non-pharmaceutical management for patients with CHF[19] and is recommended by the American College of Cardiology Foundation/American Heart Association Task Force, European Society of Cardiology[20], the National Institute for Health and Care Excellence (NICE) as well as the national guidelines.[21]

Center-based CR programs as well as home-based cardiac telerehabilitation programs has demonstrated positive effectiveness in reducing cardiovascular mortality, morbidity, hospitalization rate.[22, 23]

Recently, it has become increasingly evident that various CR interventions may also have beneficial effects in inflammatory status in patients with CHF.[1,12,13] Several high-quality randomized controlled trials (RCT) and meta-analyses highlighted the superiority of high-intensity aerobic interval training (HIAIT) compared to moderate intensity continuous training (MICT) in terms of improved FEC, left ventricular ejection fraction (LVEF), and quality of life (QoL) of patients with CHF.[24,25] However, controversies regarding the improvements in the serum levels of pro-inflammatory biomarkers, and CAMs in patients with CHF taking part in various CR interventions in which the modality intensity, duration and supervision vary still exist.[15,17] Herein we aimed to quantify the effects of various exercise-based CR interventions, namely, the group-based HIAIT and MICT on serum levels of pro-inflammatory biomarkers (CRP, TNFα), and CAMs (ICAM and VCAM) in patients with CHF.

Materials and Methods

Design and subjects

The present study is part of another larger-sized single-center, prospective, two-arm randomized controlled clinical trial carried out in Medical Center of Outpatient Rehabilitation and Sport Medicine, Plovdiv, Bulgaria, between January 2012 and June 2015.[25]

In this study one-hundred and twenty eligible subjects (70 men and 50 women) with diagnosis of stable CHF, New York Heart Association (NYHA) classes II to IIIB; left ventricular ejection fraction ≤40; and mean age 63.73 ±6.68 years were enrolled (Table I).

Specifically, sixty eligible subjects were randomized to perform HIAIT/m-Ullevaal intervention while other 60 performed the MICT intervention. Table I shows the demographic the participants clinical characteristics. A flow diagram outlining patient recruitment is shown in Figure 1. In our study we applied the NICE inclusion criteria which were: adult patients of both genders with stable CHF, New York Heart Association (NYHA) classes II to IIIB; LVEF≤40; clinically and pharmacologically stable (>3 months) prior to participation. Exclusion criteria were: diagnosis of diabetes, major surgery or recent myocardial infarction within <4 weeks, unstable angina, uncontrolled ventricular and supraventricular arrhythmias, average grade or high-grade aortic stenosis, NYHA IV class, blood pressure ≥200/110 mmHg, six-minute walking distance (6MWD) >550 m; hypertrophic obstructive cardiomyopathy, recent pulmonary embolism, deep vein thrombosis, fever, recent stroke, physical disability that precluded safe and adequate testing, and mental impairment with limited ability to cooperate (Table II). Included participants CHF etiology was: coronary artery disease (CAD) (60%), hypertension (HT) (16%), and idiopathic dilated cardiomyopathy (IDCM) (13%).

Participants were recruited from the Department of Cardiology at Medical University of Plovdiv which performed 48 sessions four times a week for twelve weeks.

Randomization

Eligible subjects after giving their consent were randomized to HIAIT/modified group-based HIAIT intervention (m-Ullevaal) and MICT groups. Participants randomization performed using a block randomization (www.randomization.com) design (by age group, sex, New York Heart Association-NYHA class, and cause of CHF). The investigator (J.P) determined the of participants eligibility and was unaware when this decision was made, of which group the subject would be allocated. Investigator (D.T) checked for the correct subjects allocation, according to the block randomization. Eligible subjects from the blocks were randomly allocated to perform HIAIT/ m-Ullevaal intervention or MICT intervention from a

randomization list that was created for this purpose. At the end of the study and after unmasking, we checked that no errors had been made in allocation.

The present study relied upon the work of a multi-professional CR team including physical and rehabilitation medicine (PRM) physicians, cardiologist, physiotherapists (PTs), exercise physiologist, clinical psychologist, social worker, dietitians, and professional nurses, all with expertise in CR. The CR sessions was mainly addressed to participants, however, also their family members may be involved given their key role in supporting patients. Four PT's, experienced in CR and exercise testing, conducted the assessments. All outcome measures before and after both CR interventions were performed by a research assistant who was blinded to the allotment.

Ethical considerations

Medical University of Plovdiv Ethics Committee approved the research protocol (No. R 3/, on May 5th, 2015). This randomized controlled trial was carried out in compliance with the Helsinki Declaration and conforms to all TIDieR and CONSORT checklists.[26, 27] Prior to enrollment in the study, all participants signed a written informed consent.

Six-minute walk test (6MWT)

The 6MWT is a valid and reliable test used to assess changes in functional capacity in patients with chronic heart disease and lung disease.[28] We performed the 6MWT according to American Thoracic Society Guidelines standardized instructions, using the 30-m corridor of Medical Center of Outpatient Rehabilitation and Sport Medicine, Plovdiv.[29] Corridor length was marked every 3 m and the turnaround point was marked with a cone. During the 6MWT, gas exchanges and ventilatory participants responses were measured continuously using a portable gas exchange analyzer VO2000 (Med Graphis, St Paul, Minnesota, USA) and the heart rate (HR) monitor (Onyx, Nonin, Plymouth, Minnesota, USA).

Laboratory Measurements

Blood samples were drawn at baseline and after 48 training sessions for determination of CRP, TNF-α, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), after an overnight fasting between 8:00 and 10:00 am. Serum was prepared within 1 hr by centrifugation at 3000 g for 10 min for all determinations. All serum samples were stored at -70-C until analysis was carried out. Serum concentrations of CRP, TNF-α, sICAM-1 and sVCAM-1, were determined by enzyme-linked immunosorbent assay (ELISA) using commercial enzyme immunoassay kits (IBL International GmbH, Hamburg, Germany, and Bender MedSystems GmbH, Vienna, Austria, respectively), as instructed by

the manufacturer. The absorption, which is proportional to the cytokines and CAMs concentration, was measured colorimetrically using TECAN ELISA reader at 450 and 630 nm.

The concentration of cytokines (the pro-inflammatory biomarkers) and CAM was calculated using a standard curve. In order to minimize run-to run variability, serial samples from the same subjects were analyzed in the same run. The inter-assay coefficients of variation in the Laboratory of Immunology, Department of Microbiology and Immunology, at the Medical University of Plovdiv Bulgaria were for CRP < 6%, TNF-α 9%, ICAM-1 5% and VCAM-1 5.5%.

Cardiac rehabilitation interventions

In the present study we applied the HIAIT/ m-Ullevaal CR intervention.[2] A detailed description of the HIAIT/m-Ullevaal intervention, as well as data on feasibility and its effects on FEC and QoL in a mixed CHF population, has been previously published elsewere.[2,26]

In brief, the group-based HIAIT/m-Ullevaal is a modified intervention consisting of three high-intensity intervals (HR max: 90%) and two intervals of moderate intensity (HR max: 70%) guided by motivational and melodious music pieces. In HIAIT/ m-Ullevaal intervention mainly three different types of exercise are included (*i.e.* muscle-strengthening, flexibility, and endurance/fitness exercises).

The participants randomized to the group-based HIAIT/m-Ullevaal intervention (N.= 60) were encouraged to achieve 90% of the maximum heart rate (HRmax), as well as participants allocated to the MICT intervention (N.=60) were encouraged to achieve 70% of the HRmax, on electromagnetically braked cycle ergometers (Pure Bike 4.1, Tunturi, Almere, Finland).

In order to determine how participants perceived their physical exercise during various training intervals of HIAIT/m-Ullevaal, we used the m-Borg's perceived exertion scale (mBPES).[30] mBPES ranging from 0 (nothing at all) to 10 (extremely severe). We encouraged the participants to achieve 5 to 7 on mBPES during high-intensity intervals of the group-based HIAIT/m-Ullevaal intervention, and 2 to 4 on mBPES (i.e. 70% of the HRmax) during the moderate intensity intervals. Participants of our study were included in CR groups consisted of 5-8 individuals. CR training sessions of both interventions (i.e. HIAIT/m-Ullevaal and MICT) consisted of 40-min daily sessions, performed 4 days/week for a period of 12 weeks. All the training sessions were supervised by PRM physician, cardiologist and PTs, latter members of CR team.[31] Twelve group-based counseling sessions were offered to the participants by health professionals of the multiprofessional CR team.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as number and percentage. Shapiro–Wilk statistic was used to test the normality. The sample size was calculated based on pilot study with 75 patients. Unpaired two-tailed *Student's t*-tests were used for analyzing the differences between groups and differences in changes from baseline between the groups. The χ^2 test was used for the comparison of categorical variables. The statistical significance level was set at $p < 0.05$ (two-tailed) for both main and interaction effects. Correlation analyses between variables were performed using Pearson's correlation coefficient.

The subgroup analyses on baseline measurements between CHF etiology groups were performed using two-tailed *t*-tests and χ^2 tests. The study time (levels: T1 and T2) was the within-subjects factor. Participants had been separated into two groups by the type of applied CR intervention *i.e.* the between-subjects factor was the type of applied intervention. In the subgroup of participants with ICDM we were obliged to set the significance level at $p < 0.03$, since this subgroup was rather small (only 16 participants) but we do not consider the slight variation in the significant level to disrupt the overall statistical evaluation and representativeness. Data were computerized and analyzed using Statistical Software Package for Social Sciences (SPSS) for Windows version 18.0.

Results

A total of 146 consecutive patients with CHF were assessed for eligibility and were allocated either to the group-based HIAIT/m-Ullevaal or to the MICT intervention. Fourteen of the eligible patients (9.58%) did not meet the inclusion criteria and were excluded. Ten patients (6.8%) refused to participate, as well as four subjects (2.7%) changed home address. Twenty-six eligible subjects dropped out (17.8%), and the final sample comprised of one-hundred and twenty patients (N. = 120) with mean age 63.73 ± 6.68 years who completed all the scheduled CR sessions (N. = 48) were used for statistical calculation. No adverse events were observed during the study period in either group (Figure1).

There were no significant between-group differences for the baseline characteristics including age, gender, FEC, QoL and any of pro-inflammatory variables among participants. Significantly greater reduction after 48 training sessions in the levels of CRP among participants performed the HIAIT/m-Ullevaal intervention were observed compared to baseline measurement and was greater than the decrease detected among the subjects performed the MICT intervention (respectively, -9.27±3.85% *vs.* -8.85±3.53%; P= 0.029; Table III).

Similarly, greater reductions in the serum levels of other pro-inflammatory biomarker investigated in the present study were detected. The serum levels of TNF-α decreased by -8.93±3.51% among participants performed HIAIT/m-Ullevaal intervention (respectively, 2.69±0.7 to 2.45±0.53 pg/ml, P<0.05) and by -7.87±3.21% among subjects performed MICT (respectively, 2.46±0.57 to 2.26±0.46 pg/ml, P<0.05; Figure 2).

As shown in Figure 3, significantly greater decrease in the levels of sICAM was measured in participants performed MICT CR intervention, compared to the decrease measured in the participants randomized to perform the HIAIT/ m-Ullevaal intervention (respectively, 12.76±4.68% *vs*. -11.52±4.84, P<0.05). Undoubtedly, statistically greater decrease in sICAM levels was found in a small subgroup consisted of 16 participants with IDCM, compared with the decrease achieved among participants performed MICT intervention (respectively, -12.15±8.77 *vs*. -11.1±9.45, P<0.03; Table IV; Figure 4). Subgroup analysis demonstrates significant reduction in the levels of CRP (P = 0.188), TNF-α (P=0.149), and sICAM-1 levels (P= 0.228), sVCAM-1 (P= 0.205), compared to the participants performed MICT (Table IV). In Table III is shown the significant reduction detected in the circulating levels of sVCAM in patients performed the group-based HIAIT/m-Ullevaal intervention respectively, -7.53±3.13%, which was greater compared to the decrease observed in the MICT intervention, respectively 6.88±2.62% (Figure 4).

Significant inverse correlation was found between the percentage reduction in CRP (r = -0.72, P< 0.05), and the improvements in 6MWT, as well as the levels of VCAM-1 (r = -0.68, P < 0.05), indicating that the attenuation of both, CRP and VCAM-1 may contribute to the improvement in FEC achieved due to HIAIT/m-Ullevaal in patients with CHF. Furthermore, weak but significant correlation was found in the MICT group between the percentage reduction in sICAM levels and the peak oxygen uptake (r = 0.34, P < 0.05; Table III).

Discussion

Exercise-based interventions have been widely acknowledged as non-pharmacological anti-inflammatory and immune modulating strategies in patients with CHF.[18,19,21] In accordance with what was expected, both group-based CR interventions resulted in a reduction in the inflammatory state, evidenced by diminished levels of selected pro-inflammatory biomarkers and participants CAMs. Improvements in circulating levels of pro-inflammatory biomarkers and adhesion molecules in patients with CHF performed different exercise-based interventions has been referred in several previous studies. [9,10,14,15] Koh *et al*. showed that the changes in levels of pro-inflammatory biomarkers and CAMs are depending on a training modality applied.[32]

The increased levels of CRP have been associated with reduced exercise capacity or with poor prognosis in patients with CHF.[33] The leading role of CRP as an inflammatory biomarker in cardiovascular disease is not primarily based on its pathogenic properties in these disorders, but rather on its ability to reflect upstream inflammatory activity.[34] A recent meta-analysis evaluating the effects of different training modalities on circulating concentrations of pro-inflammatory biomarkers and CAMs showed a borderline statistically significant improvement in CRP in pooled data from three studies with CHF patients.[1] The decrease of CRP levels among participants performed HIAIT/m-Ullevaal intervention was significant (-9.27%) compared to baseline measurement, and was greater than the decrease detected among the subjects performed the MICT intervention, respectively -8.85% (Table III). Strong evidence provided from previous studies confirmed that aerobic exercise-based interventions with or without resistance training may reduce significantly the serum levels of CRP in patients with CHF.[35, 36]

TNF-α was another pro-inflammatory biomarker which was found to be elevated among participants of our study. The beneficial effects of exercise training on pro-inflammatory biomarkers supporting our results has been reported in several previous studies.[13,35] de Meirelles *et al*., referred that, chronic exercise resulted in a reduction in the inflammatory state effects in patients with CHF, evidenced by diminished systemic biomarkers of inflammation levels, CRP, TNF-α and fibrinogen.[36] In contrast Byrkjeland *et al*., referred limited effects to pro-inflammatory biomarkers in patients with CHF performed group-based high intensity exercise training program, offered twice a week for four months.[17] We found that all outpatients of our study performed both group-based interventions had significant improvements in the serum TNF-α levels (Table III). However, the decrease in TNF-α levels observed among participants performed HIAIT/m-Ullevaal intervention was significantly greater compared to the decrease detected among participants performed MICT intervention, (respectively, - 8.93% *vs*- 7.78%; Figure 2).

Individuals with a certain type of cardiometabolic diseases, such as CHF, myocardial infarction, or type 2 diabetes mellitus, had reduced sICAM-1, sVCAM-1 following moderate-intensity exercise training for 8–12 weeks.[15,37,38] Adamopoulos *et al*., have demonstrated significant reductions in several pro-inflammatory biomarkers of inflammation and adhesion molecules such sICAM-1, and sVCAM-1 with a 12-week home-based, moderate intensity exercise training program in patients with CHF.[9] Not surprisingly, significant decrease in CAMs levels compared with their baseline values was observed in our study. Although, the detected decrease in sICAM serum levels were significantly greater in patients with CHF performed the group-based MICT intervention (-12.76±4.68%) compared to the decrease observed in the HIAIT/m-Ullevaal (-11.52±4.84%) (Figure 3).

In contrast, we observed significantly greater decrease in sICAM, in a small subgroup of patients with IDCM consisted of sixteen participants (N. =16), compared to the decrease achieved in eight participants (N. =8) with IDCM performed MICT (respectively, -12.15±8.77% *vs*-11.1±9.45; Table IV). (Table IV). The significantly greater reduction in sICAM among participants with IDCM of our study may be attributed with the pro-inflammatory pattern of this subgroup compared to the other subgroups of our study, *i.e.* hypertensive CHF and CAD. Our results are in line to the findings of Aksoy *et al*. [15] which referred significantly decreased levels of sICAM-1 in CHF patients performed 10-weeks of supervised moderate-intensity exercise intervention, as well as with results reported in the study of Byrkjeland *et al*.,[17] where has been demonstrated a significant reduction in sICAM-1 in subgroup of patients with IDCM. Contrary to findings reported in other studies, we observed a significantly greater reduction in circulating levels of sVCAM in patients performed group-based HIAIT/m-Ullevaal intervention compared to the decrease observed in MICT intervention (respectively, -7.53±3.13%) *vs* -6.88±2.62%; Table III).[15, 17]

According to the current literature, CAMs can be affected by the type and intensity of exercise intervention performed.[32] We consider group-based HIAIT/m-Ullevaal intervention as strong immune stimulator and one of the potential underlying mechanisms for the CAMs metabolism. Although, we don't overlook the importance of age, ejection fraction and CR interventions duration as factors that may contributed to achieve the significant anti-inflammatory effects among participants of our study. To our knowledge, both immunological and inflammatory processes are age-dependent and appear to play pivotal role in the development and CHF progression.[39] Moreover, ageing impacts the exercise response and the implications on the declining FEC of patients with CHF are significant.[40] However, it is important to be noted that the subjects participated mean age in our study was 63 years, and they were significantly younger compared with individuals with CHF included in earlier studies provided ambiguous results.[17] From the other hand, it seems that the different etiologies of CHF may also affect the response to the group-based HIAIT/ m-Ullevaal intervention on the pro-inflammatory biomarkers and CAMs. Nevertheless, further research regarding the anti-inflammatory and immune-modulatory group-based HIAIT/ m-Ullevaal intervention effects in a variety of CHF etiologies is required.

Limitations

Our study had some limitations that should be mentioned. First, this was a prospective, single-center randomized controlled trial performed in a cohort with CHF of Plovdiv area. Generalizing results to other populations should therefore be done with caution. A main study limitation was the relatively small sample of IDCM sub-group, respectively 13%, which not allowed to perform separate multiple regression analyses, as well as to identify differences in confounding factors between sub-groups. A greater IDCM sub-group is needed in order to increase the confidence in the observations made, as well as to generalize the findings in this subgroup. Additionally, the quite high dropout rates (17.8%), so as to decrease the statistical power of our results. Lastly, another limitation in our study may be the lack of cardiac telerehabilitation application as alternative option to in-person therapy that should significantly reduce the dropout rates. This is also supported by the European Association of Preventive Cardiology, which considers telerehabilitation to be relevant for all patients with cardiovascular disease who cannot regularly visit CR centers.[23]

Conclusions

The findings of our study suggest a statistically significant reduction in selected levels of pro-inflammatory biomarkers and adhesion molecules observed after 48 training sessions in both group-based interventions. PRM physicians, cardiologists, as well as all health-care professionals involved in CR are encourage to prescribe HIAIT/m-Ullevaal intervention in patients with CHF. Further research is required to examine the anti-inflammatory and immune-modulatory effects of this group-based intervention in a variety of CHF etiologies.

NOTES

Conflicts of interest.– The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Data statement.– Restrictions apply to the availability of data generated and analyzed in the current study; these data are property of Medical Center of Outpatient Rehabilitation and Sport Medicine, Plovdiv, Bulgaria.

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Table I.—*Participants baseline demographic and clinical characteristics of the participants at baseline.*

Variable	**HIAIT/ m-Ullevaal (N. =60)**	**MICT (N. =60)**
Age (years)	63.65 ±6.71	63.82± 6.71
Gender (men/women)	35/25	35/25
6MWT (m)	440.58±39.7	442.90±42.5
mBPES	6.60±0.64	6.42±0.62
$VO_{2\ peak}$ (mL/kg/min)	13.49±3.7	12.51±3.5
MLHFQ score	36.88±5.1	37.40±7.7
NYHA class II/III	48/12	46/14
Diagnosis		
Coronary artery disease	36 (60%)	36 (60%)
Hypertension	16 (26.7%)	16 (26.7%)
ICDM	8 (13.3	8 (13.3%)

Data presented as mean ± SD or number of patients (percent).

HIAIT: high-intensity aerobic interval training; MICT: moderate intensity continuous training; 6MWT: six-minute walk test; mBPES: modified Borg's Perceived Exertion Scale; VO2peak: peak oxygen uptake; MLHFQ:

Minnesota living with the Heart Failure Questionnaire; NYHA: New York Heart Association; IDCM: idiopathic dilated cardiomyopathy.

Table II.—*Inclusion and Exclusion NICE Criteria.*

Indications	Contraindications
Primary: • Detection of coronary artery disease (CAD) in patients with chest pain (chest discomfort) syndromes or potential symptom equivalents • Evaluation of anatomic and functional severity of CAD • Prediction of cardiovascular events and all-cause death • Evaluation of physical capacity and effort tolerance • Evaluation of exercise-related symptoms • Assessment of chronotropic competence, arrhythmias, and response to implanted device therapy • Assessment of the response to medical interventions **Additional:** • Development of the exercise plan or prescription • Response to medication • Evaluation of perioperative risk for non-cardiac surgery	**Absolute contraindications:** • Acute myocardial infarction within 2 days • Ongoing unstable angina • Uncontrolled cardiac arrhythmia with hemodynamic compromise • Active endocarditis • Symptomatic severe aortic stenosis • Decompensated heart failure • Acute pulmonary embolism, pulmonary infarction, or deep vein thrombosis • Acute myocarditis or pericarditis • Acute aortic dissection • Physical disability that precludes safe and adequate testing **Relative contraindications:** • Known obstructive left main coronary artery stenosis • Moderate to severe aortic stenosis with uncertain relation to symptoms • Tachyarrhythmias with uncontrolled ventricular rates • Acquired advanced or complete heart block • Hypertrophic obstructive cardiomyopathy with severe resting gradient • Recent stroke or transient ischemic attack • Mental impairment with limited ability to cooperate • Resting hypertension with systolic or diastolic blood pressures >200/110 mmHg • Uncorrected medical conditions, such as significant anaemia, important electrolyte imbalance, and hyperthyroidism

Table III. — *Levels of the pro-inflammatory biomarkers (CRP, TNF-α) and CAMs (sICAM, sVCAM) in group-based HIAIT/ m-Ullevaal and MICT intervention at baseline and after 12 weeks.*

CR interventions	**HIAIT/m-Ullevaal**		**(%) change (95% CI)**	**p**	**MICT**		**(%) change (95% CI)**	**p**	**P-value**
Variable	Baseline (T1)	Follow-up (T2)			Baseline (T1)	Follow-up (T2)			
CRP (mg /L)	4.66 ± 1.3	4.23± 1.05	-9.27±3.85 (-13.12 ÷-5.42)	0.05	4.2± 1.02	3.83± 0.93	-8.85±3.53 (-12.38 ÷-5.32)	0.05	0.029
TNF-α (pg/ml)	2.69±0.7	2.45±0.53	-8.93±3.51 (-12.24÷-5.13)	0.05	2.46±0.57	2.26±0.46	-7.87±3.21 (-11.08÷-4.66)	0.05	0.036
sICAM-1 (pg/ml)	301±108	266.3 ±82	-11.52±4.84 (-16.36÷-6.68)	0.05	344±120	300.1±89.6	-12.76±4.68 (-17.44 ÷-8.08)	0.05	0.034
sVCAM-1 (pg/ml)	1348± 301.6	1246.5± 250.8	-7.53±3.13 (-10.66÷-4.40)	0.05	1247± 234	1161 ±195	-6.88±2.62 (-9.50 ÷-4.26)	0.05	0.040

Data presented as mean ± SD or number of patients (percent).

CR; cardiac rehabilitation; HIAIT: high-intensity aerobic interval training; MICT: moderate intensity continuous training; CRP: C-reactive protein; TNF-α: tumor necrosis factor-alpha; sICAM-1: soluble intercellular adhesion molecule; sVCAM-1: soluble vascular cell adhesion molecule.

Table IV. —*Levels of the pro-inflammatory biomarkers (CRP, TNF-α) and CAMs (sICAM, sVCAM in the subgroup with IDCM at baseline and after 12 weeks.*

IDCM group	**HIAIT/m-Ullevaal**		(%) change (95% CI)	**p**	**MICT**		**(%) change (95% CI)**	**p**	**p-value**
Variable	Baseline (T1)	Follow-up (T2)			Baseline (T1)	Follow-up (T2)			
CRP (mg /L)	3.7 ± 0.68	3.35± 0.59	-9.52±7.67 (-17.19 ÷-1.85)	0.3	4.16 ± 0.77	3.78 ± 0.65	-9.16±7.63 (-16.79÷-1.53)	0.3	0.188
TNF-α (pg/ml)	1.93±0.36	1.76±0.3	-8.96±7.65 (-16.61 ÷-1.31)	0.3	2.19±0.4	2.0±0.33	-8.71±7.46 (-16.17 ÷-1.25)	0.3	0.149
sICAM-1 (pg/ml)	298±63	263±54	-12.15±8.77 (-20.92 ÷-3.38)	0.3	336±79	299±62.5	-11.1±9.45 (-20.55÷-1.65)	0.3	0.228
sVCAM-1 (pg/ml)	1332±217.2	1222 ± 183.6	-8.23±6.73 (-14.96 ÷-1.50)	0.3	1206± 177	1113.8 ±139	-7.64±5.88 (-13.52÷-1.76)	0.3	0.205

Data presented as mean ± SD or number of patients (percent).

IDCM: idiopathic dilated cardiomyopathy; HIAIT: high-intensity aerobic interval training; MICT: moderate intensity continuous training; CRP: C-reactive protein; TNF-α: tumor necrosis factor-alpha; sICAM-1: soluble intercellular adhesion molecule; sVCAM-1: soluble vascular cell adhesion molecule.

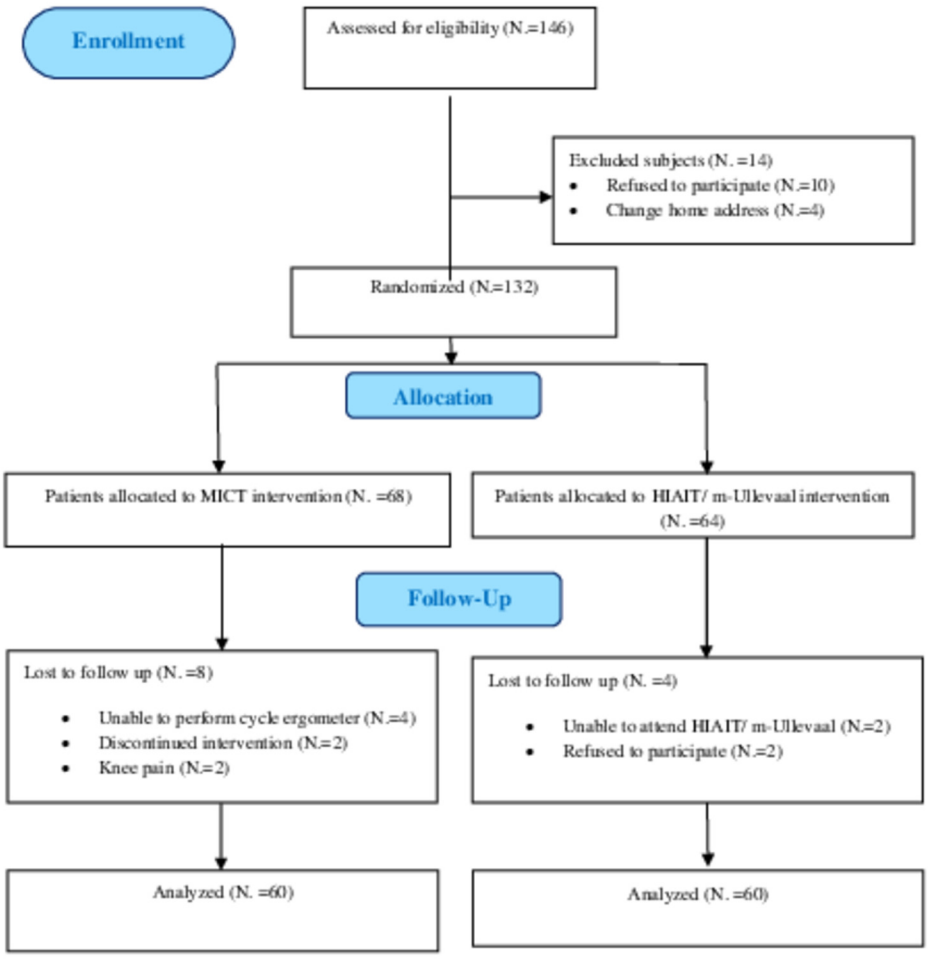


Figure 1.—*Flow chart of study and number of patients in follow-up.*

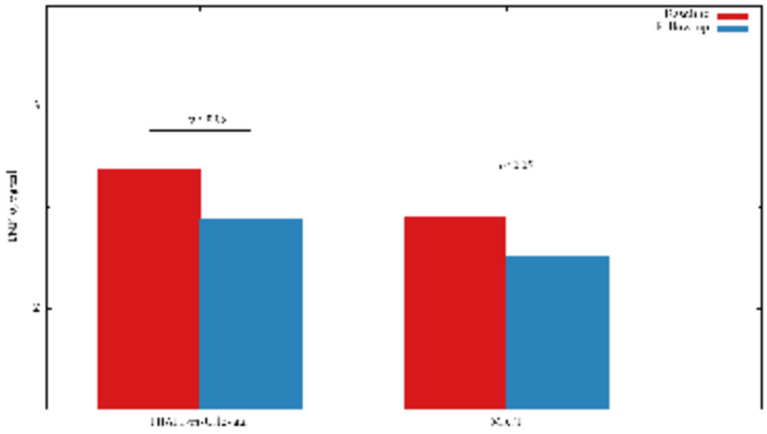


Figure 2.—*Mean percentage changes in TNF-α, among participants following HIAIT/m-Ullevaal and MICT interventions.*

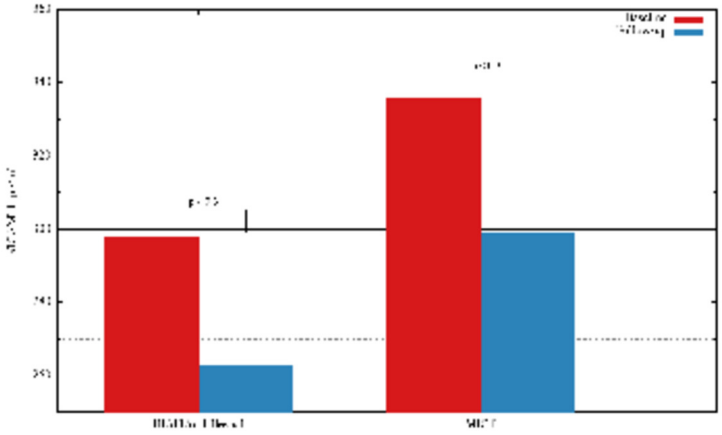


Figure 3.—*Mean percentage changes in sICAM-1 among participants following HIAIT/m-Ullevaal and MICT interventions.*

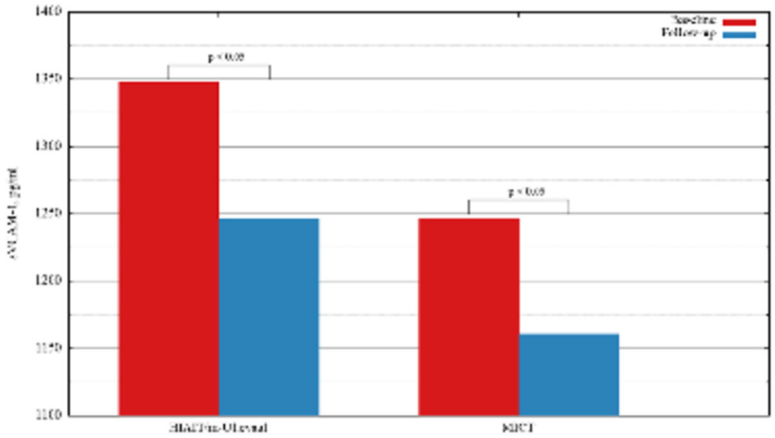
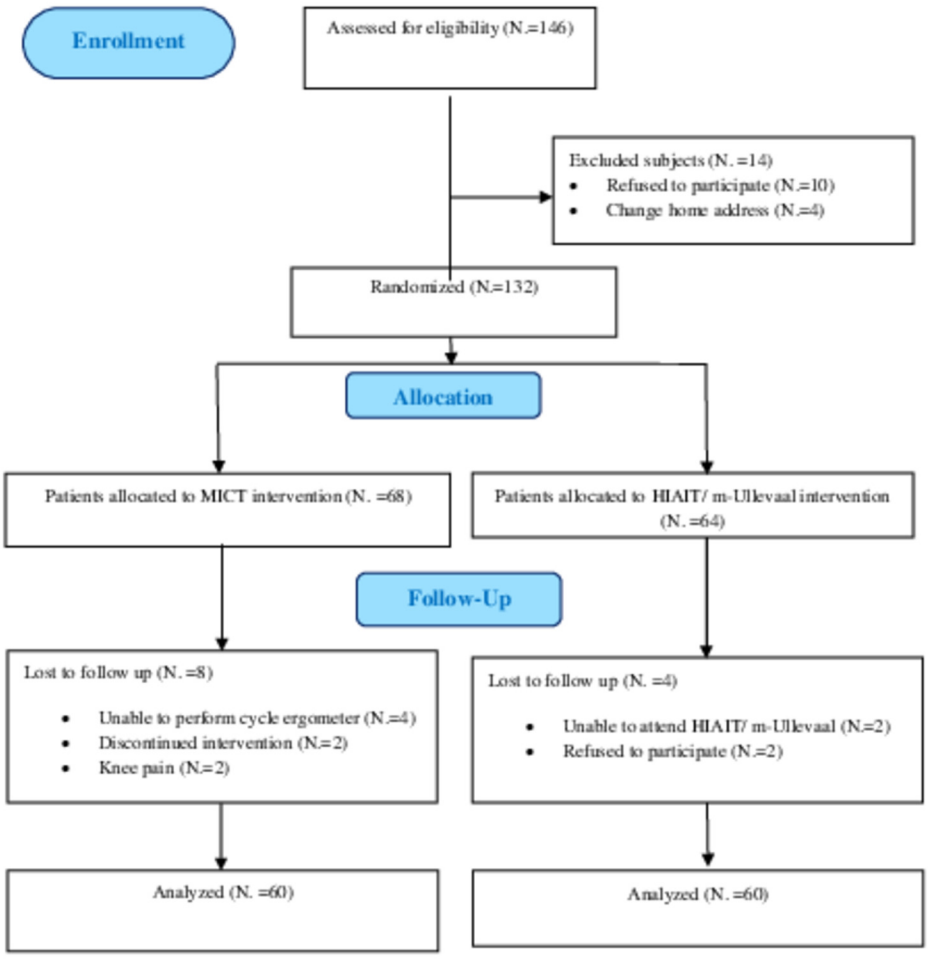


Figure 4. — *Mean percentage changes in sVCAM-1among participants following HIAIT/m-Ullevaal and MICT interventions.*



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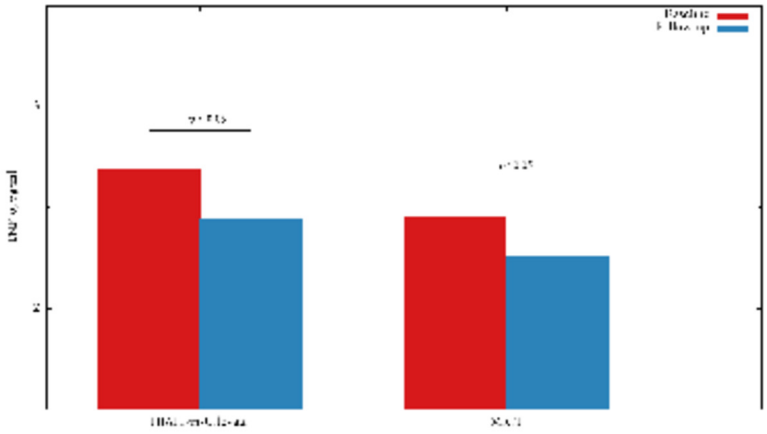

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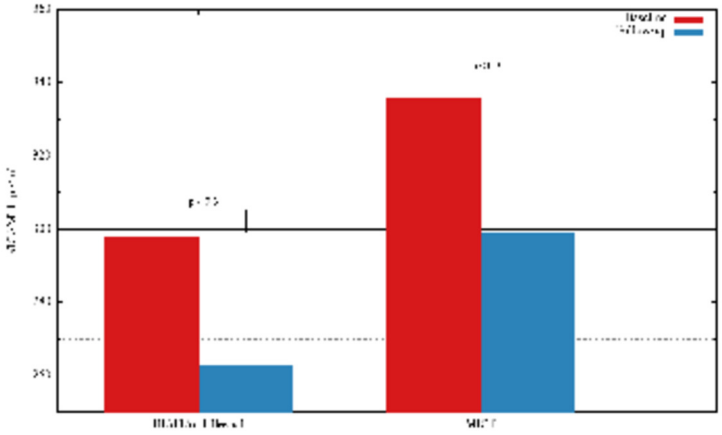
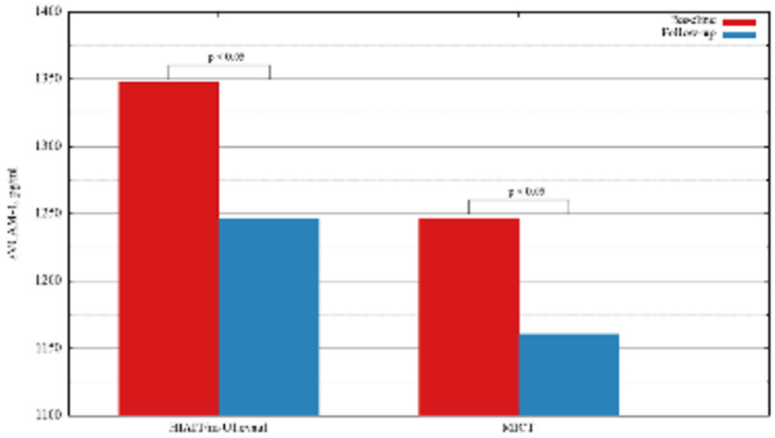


Figure 3.—*Mean percentage changes in sICAM-1 among participants following HIAIT/m-Ullevaal and MICT interventions.*



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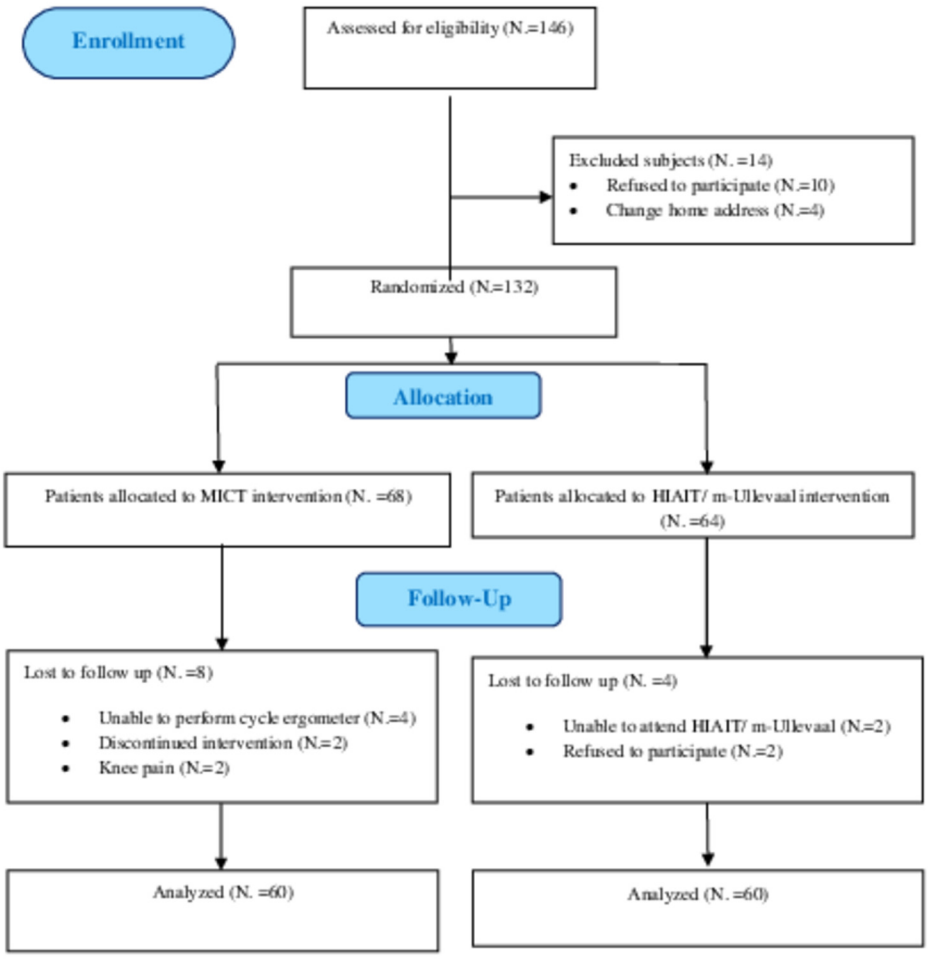

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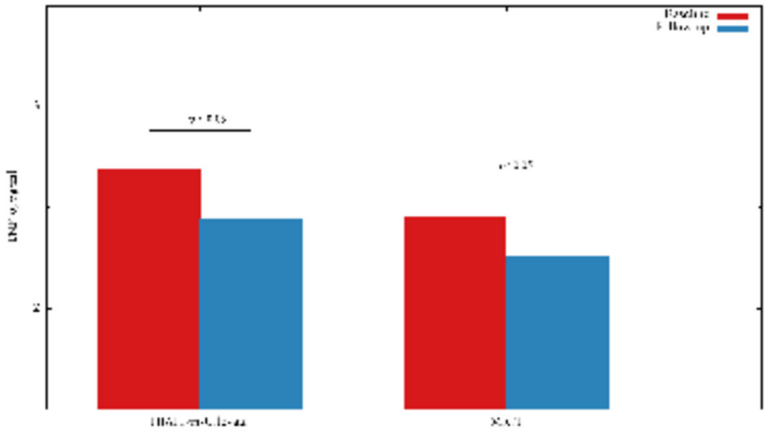

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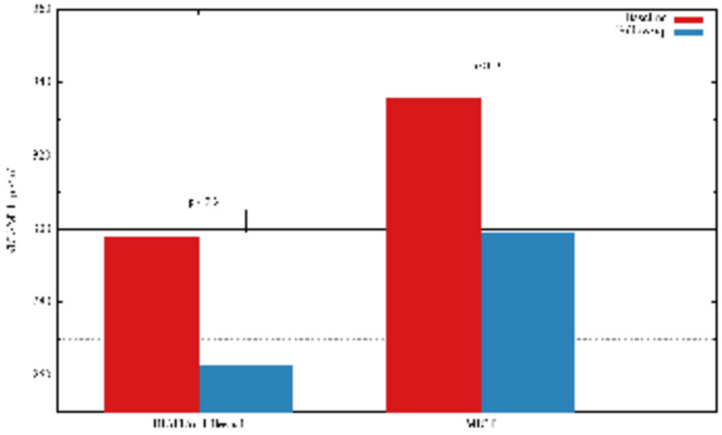

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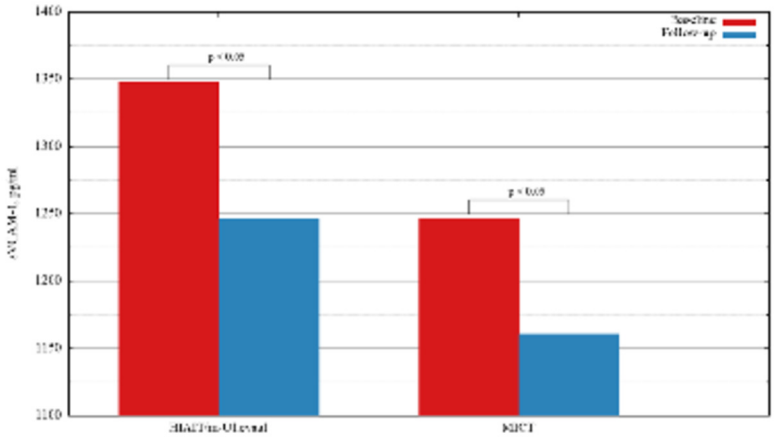

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