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INTRODUCTION

Patients who adhere to more comprehensive professional lifestyle intervention (*i.e.,* smoking cessation, adequately designed and supervised exercise program and diet recommendations) have a 54% lower risk of recurrent events six months after a myocardial infarction (MI),[1] and their quality of life and longevity increase.[2]

Previous studies support the beneficial effect of the Mediterranean Diet (Mediet) combined with regular exercise for the primary prevention of cardiovascular disease[3] and reduction of cardiovascular risk,[4,5] despite the amount of inter-study heterogeneity observed.[6] Along these lines, a recent meta-analysis has demonstrated no improvement in all-cause mortality from patients participating in an exercise-based cardiac rehabilitation program when compared to the non-exercise control group.[7] However, data from studies included in this review were based on a wide range of clinical environments, and the intervention ranged greatly in quality (*i.e.,* participants may not have received an adequate dose of exercise).[7] High-intensity aerobic interval training (HIIT) has been found to be more effective than moderate-intensity continuous aerobic exercise training in improving cardiac and vascular functions, aerobic capacity, post-exercise heart-rate recovery and psychological states in patients with coronary artery disease (CAD).[8-14] Nevertheless, the SAINTEX-CAD study observed similar improvement in exercise capacity, and peripheral function after 12-week HIIT and moderate-intensity continuous aerobic exercise training intervention in CAD patients,[15] and a systematic review found that the superiority of HIIT disappeared when isocaloric protocols were applied in these patients.[16]

On the other hand, low-volume HIIT protocols are time-efficient strategies that have been shown to be effective in both healthy populations[17-19] and individuals with health conditions such as CAD,[20] Type II diabetes mellitus,[21-23] and primary hypertension.[24] Taking into account that "lack of time" is one of the more common barriers for people considering initiation of a supervised exercise program, low-volume HIIT could be an interesting strategy if the resultant physiological benefits are comparable to high-volume HIIT.

It is very well known that higher cardiorespiratory fitness (CRF) (*i.e.,* peak oxygen uptake, $\dot{V}O_{2peak}$) is linked with a lower risk of early death after a first MI,[25] and also the importance of the "fat-but-fit" paradigm on mortality risk among patients with CAD.[26] Therefore, the purpose of this study was to analyze the changes in CRF and body composition following two different (low-volume *vs*. high-volume) 16-week aerobic HIIT programmes performed twice a week compared to an attention control (AC) group, all combined with Mediet recommendations, in patients after an MI. We hypothesized that low-volume HIIT would provide sufficient stimulus to get similar improvements as high-volume HIIT on CRF and body composition.

METHODS

The INTERFARCT study is a single-blind, randomized controlled, three-arm parallel trial comparing the effects of two-different 16-week HIIT aerobic exercise programmes (performed two days/week) combined with Mediet recommendations in patients after an MI (Clinical Trials.gov ID: NCT02876952). The study complied with the World Medical Association Declaration of Helsinki on ethics in medical research. The protocol and informed consent procedures were approved by the ethics committee of the university (UPV/EHU, CEISH, 2016) and the ethics committee of clinical investigation of the hospital (CEIC 1462), and all participants provided written informed consent before the clinical and physiological examination. Cardiologist staff was blinded to the participant randomization process. The design, selection criteria, and procedures for the INTERFARCT study have been detailed previously.[27]

Two hundred twenty-four patients were assessed for eligibility (Supplemental Digital Content, SDC). However, after exclusion for not meeting the inclusion criteria and/or refusal to participate, only 70 non-Hispanic white patients (n=59 men and 11=women) with the diagnosis of MI according to criteria of "Third Universal definition of myocardial infarction" and clinical classification of MI type 1, called "Spontaneous myocardial infarction,"[28] were enrolled in the study from February 2016 to December 2017.

The measurements for the study were taken before (T1) and after (T2) the intervention period (16-weeks) (SDC). The post-intervention assessment procedures were scheduled the following week after finishing the 16-week intervention period. **Anthropometry and Body Composition**

Stature (SECA 213, Hamburg, Germany), total body mass (SECA 869, Hamburg, Germany), and waist and hip circumferences (SECA 200, Hamburg, Germany) were measured before the cardiopulmonary exercise test to calculate the waist-to-hip ratio (WHR). Further, bioelectrical impedance (Tanita, BF 350, Tokyo, Japan) was used to estimate fat-free mass, and fat body mass.

Cardiorespiratory fitness

As described previously,[27] a peak, gradual and symptom-limited cardiopulmonary exercise test (*i.e.,* starting at 0W with 10W gradual increments every minute) on a cycle ergometer (Lode Excalibur Sport Cycle, Groningen, The Netherlands) was performed. Twelve-lead electrocardiogram monitoring and breath-by-breath gas exchange measurements (Ergocard Medisoft, Belgium, Ref. USM001 V1.0) were recorded continuously, and blood pressure was measured every 2 min. Achievement of $\dot{V}O_{2peak}$ criteria has previously been defined.[29] Ventilatory thresholds (*i.e.,* VT1 and VT2) were assessed by standardized methods using ventilatory equivalents.[29] The three exercise intensity domains (*i.e.,* R1-light to moderate; R2-moderate to high; and R3-high to severe) were determined with the two VT or percentages of heart rate reserve when VT2 was not possible to identify.[27,29]

Intervention

All participants received Mediet pattern recommendations.[27] The AC group was encouraged to maintain regular physical activity in order to keep ethical procedures regarding health.[27,30,31] The training intervention for low- and high-volume HIIT was previously described.[27] In short, the participants trained for two non-consecutive days per week for 16 weeks, under supervision by an exercise specialist. The principal portion of the training session consisted of aerobic exercises; *i.e.,* one day of the week on the treadmill (intervals of 4 min at R3 followed by 3 min at R2), and the second one on the exercise bike (intervals of 30 s at R3 followed by 60 s at R2) developing progressively both the volume (*i.e.,* 20 to 40 min in high-volume HIIT, whereas in low-volume HIIT the duration was always 20 min) and intensity (BH Fitness equipment). Intensity was individually tailored to heart rate at moderate (R2) or vigorous (R3) intensities, adjusting the speed and incline of the treadmill, or the power (W) and speed on the exercise bike, to achieve the planned target heart rate. Supervised exercise training protocols have been previously explained in full.[27]

Considering the mean $\dot{V}O_{2peak}$ (1.9 $L \cdot min^{-1}$) or peak metabolic equivalent (6.6 METs) at baseline for all participants, the total work performed by the two exercise groups was calculated using the total amount of energy expended during the different aerobic exercise programs over a period of 1 wk, the combination of frequency, intensity, type and time was taking into account.[32] Thus, the moderate intensity at R2 was taken as 70% of $\dot{V}O_{2peak}$ (1.3 $L \cdot min^{-1}$) or MET_{peak} (4.6 METs) and the high intensity at R3 as 90% of $\dot{V}O_{2peak}$ (1.7 $L \cdot min^{-1}$) or MET_{peak} (5.9 METs). As such, the low- and high-volume HIIT groups performed 20 and 40 min twice per week, respectively; exercising one day on the treadmill (low-volume HIIT: 2x4 min at R3 and 12 min at R2; high-volume HIIT: 4x4 min at R3 and 24 min at R2, representing ~131 kcal and ~263 kcal, respectively) and one day on the exercise bike (low-volume HIIT: 8x30 sec at R3 and 16 min at R2, high-volume HIIT: 16x30 sec at R3 and 32 min at R2, representing ~104 kcal and ~210 kcal, respectively). In all, it represented ~235 kcal/week for low-volume HIIT *vs.* ~473 kcal/week for high-volume HIIT. Compliance for the exercise intervention was set at at least 80% of a total of 32 sessions.

Statistical analysis

The required sample size was determined for the primary outcome variable ($\dot{V}O_{2peak}$). It was identified that adequate power (0.80) to evaluate differences in our design consisting of three experimental groups would be achieved with 177 people (50 in each group, α=0.05, effect size f=0.23).[27] Therefore, as the sample size was too small (n=70) to have adequate power for statistical significance the current report is considered a pilot study. Descriptive statistics were calculated for all variables. Data are expressed as means ± standard deviations and the range. All variables that were not normally distributed using a Kolmogorov-Smirnov were log transformed prior to any analysis. Analysis of variance was used to determine if there were significant pre-intervention differences among groups. The comparison of frequencies in categorical variables among groups was performed using the Chi Square test. A 2-sample *t*-test was used to determine whether there was a significant difference in the recorded data between preand post- intervention within each group. Analysis of covariance was used to examine the delta (Δ) score classified by group (attention control, high-volume HIIT, low-volume HIIT), adjusting the analysis for age, sex and initial value of each of the dependent variables. Helmert contrasts were performed to analyze the differences between the two exercise groups pooled together and the AC group. Bonferroni correction was used to determine the level of significance when a significant main effect was found. Data were analyzed according to the intention-to-treat principle. Statistical significance was set at $P<0.05$. All statistical analyses were performed with SPSS version 22.0.

RESULTS

Baseline characteristics (T1)

Participants and medications were classified by group and are presented in Table 1. The participants' mean age ± standard deviation was 58.4±8.5 yrs, with less number of women (16%) than men (84%). At T1, 84% of participants suffered from hypertension, 29% from type 2 diabetes mellitus, 89% from dyslipidemia, 80% were smokers, 13% had sleep apnea, and 38% were consuming more than 14 drinks of alcohol per week. According to the American College of Sports Medicine, participants of the present study were classified as having "poor" CRF level[33], taking into account $\dot{V}O_{2peak}$ values (23.1±7.4 and $mL{\cdot}kg^{-1}{\cdot}min^{-1}$). Concerning the medication, all participants (n=70) were under pharmacological treatment, irrespective of groups. Regarding medication type, 91% of participants took beta-blockers, 87% angiotensin-converting enzyme inhibitors/angiotensin receptor antagonist, 94% aspirin, 57% clopidogrel or similar, 4% anticoagulants, 18% calcium antagonists, 21% diuretics, 99% statins, and 23% hypoglycaemic agents. There were no significant between-group differences ($P>0.05$) observed for body composition, anthropometrics, CRF and pharmacologic treatment.

There was only one difference in rest systolic blood pressure (mmHg) with smaller (P=0.003) values in the AC group compared with high-volume HIIT (mean difference=13.286, 95%CI=22.694-3.877 mmHg).

Follow-up changes (T2)

At T2, 15 participants were dropouts. Therefore, the total sample for statistical analysis after intervention was 55 (SDC). At follow-up, some anthropometric changes were shown in the exercise groups (Table 2). Both groups reduced waist circumference significantly (low-volume HIIT, Δ -4%, p<0.05, high-volume HIIT, Δ -2%; P<0.001). The waist-to-hip ratio decreased only in low-volume HIIT (Δ -4%, P<0.01). Body mass, fat free mass and fat body mass did not show any significant change at T2. Following Bonferroni correction, there were no significant between-group differences in any anthropometric and body composition variables.

Regarding physiological changes related to CRF, as shown in Table 2, $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) and MET increased significantly at T2 (low-volume HIIT, Δ 15%; P<0.01 and high-volume HIIT, Δ 22%; P<0.001). Further, both groups increased at least one MET after intervention (Table 2). However, improvements in VT ($mL \cdot kg^{-1} \cdot min^{-1}$) with higher values were observed only in high-volume HIIT for VT1 (Δ 12%, P=0.009) and for VT2 (Δ 16%, P=0.003). A significant increase was also observed following training for exercise groups in cardiopulmonary exercise test duration (min) (low-volume HIIT, Δ 17%, P<0.001 and high-volume HIIT, Δ 14%; P<0.001) and $Power_{peak}$ in the cycle ergometer (W) (low-volume HIIT, Δ 18%, P<0.001 and high-volume HIIT, Δ 15%, P<0.001). In contrast, no significant changes were seen in the AC group for any of the physiological variables studied. Following Bonferroni correction, there were significant between-group differences. Thus, the HIIT groups showed significant improvement in $\dot{V}O_{2peak}$ (P<0.001) compared with the AC group (low-volume HIIT, mean difference=2960, 95% CI=7.497-1.577 mL·kg^{-1}·min^{-1}; and high-volume HIIT, mean difference=4.546, 95% CI=9.051-0.041 mL·kg^{-1}·min^{-1}) and MET (*P*<0.001). There were also improvements in the secondary variables such as $Power_{peak}$ (low-volume HIIT, mean difference=22.200, 95% CI=39.861–4.539 W; and high-volume HIIT, mean difference=20.847, 95% CI=38.250-3.444 W) and exercise duration (low-volume HIIT, mean difference=2.247, 95% CI=0.490–4.00 min; and high-volume HIIT, mean difference=2.060, 95% CI=0.331-3.789 min). No significant differences between HIIT groups were found in any of the studied variables.

Angiotensin-converting enzyme inhibitors/angiotensin receptor antagonist dose was changed in five patients during the intervention period: the dose was reduced in 3 low-volume HIIT and 2 high-volume HIIT participants. Beta-blocker dose was not changed in any of the participants.

During the intervention and training sessions there were no adverse events reported.

DISCUSSION

The present study examined the effects of low- and high-volume HIIT in comparison to AC, combined with Mediet recommendations in all three groups, on body composition and CRF in patients after suffering an MI. Primarily, this study showed that both HIIT exercise protocols induced positive changes in CRF and waist circumference to a similar extent, proving the efficiency of low-volume HIIT. However, significant improvements in VT1 and VT2 values (submaximal aerobic variables) were observed only in the high-volume HIIT, highlighting its greater benefits. No improvements were found, however, in body composition and CRF for the AC group, suggesting that supervised exercise programs lead to better health-related results than only physical activity recommendations.

Bearing in mind the link between CRF and survival time following an MI,[34] one of the main challenges in secondary prevention after an acute MI is to improve functional capacity. Therefore, finding the most efficient way to achieve this [*i.e.,* the precision to exercise-based strategies applying the Frequency, Intensity, Type, Time principle], is a clinically relevant concern.[32] In the present study, both HIIT groups responded to the exercise dose to improve CRF (*i.e.,* relative $\dot{V}O_{2peak}$ and MET) post-training (low-volume HIIT, Δ 15%; $P<0.01$ and high-volume HIIT, Δ 22%; $P<0.001$), with a non-significant between-group difference ($P=0.016$, ES=0.114, Table 2), even with an exercise-volume difference between groups of 50% (*i.e.,* low-volume=20min *vs.* high-volume=40min). Previous studies on individuals with CAD have found that for a fixed volume of exercise, the intensity is positively associated with greater improvement in CRF compared to a lower-intensity load.[11,35,36] This confirms that lower exercise-intensities may not be sufficient to improve CRF in a substantial proportion of sedentary adults.[37] However, the current study has indeed provided evidence whether exercise associated with CRF response is more dependent on exercise volume or intensity. Thus, a low-volume HIIT program (*i.e.,* less than 10 min per session exercising at high-intensity zone) performed twice a week seems to be an efficient stimulus to obtain a clinically relevant CRF improvement in individuals after an MI. This result reinforces the idea of "less is more" in this population, after observing similar results in obese participants with primary hypertension with no previous cardiovascular event.[24]

The mechanisms underlying the beneficial effect of low-volume HIIT could be multifactorial (*i.e.,* skeletal muscle and cardiovascular system).[38,39] Thus, studies specifically applying low-volume HIIT in different populations following training have shown increases in regulators of mitochondrial biogenesis via co-activation of transcription factors linked to mitochondrial gene expression,[19] positive changes in the myocardial mass leading to physiological cardiac hypertrophy,[40] better autonomic profile,[41] and even improvements of endothelium-dependent brachial artery flow-mediated dilation and significant outwards artery modelling.[42] Following these results and observations, it seems clear that low-volume HIIT may represent a safe, potent, and time-efficient exercise strategy in clinical practices such as cardiac rehabilitation programs. This would also facilitate concurrent resistance training and low-volume HIIT in the same session, as recommended by international consensus.[43]

On the other hand, the fact that after intervention non-significant improvements related to CRF were found in the AC group shows that general physical activity recommendations for this population may not be enough to improve functional capacity. This evidence demonstrates that supervised and individually designed exercise led by qualified exercise specialists is of clinical relevance. Our results are even more reinforced after analyzing other variables related to CRF, such as MET, total exercise time on the cardiopulmonary exercise test (min), and $power_{peak}$ (W) (Table 2). Thus, only supervised exercise groups presented positive and significant changes after intervention in the aforementioned variables. Further, it is particularly noteworthy that both HIIT groups incremented at least one MET after intervention (low-volume HIIT, 6.6 *vs.*7.6; and high-volume HIIT, 6.6 *vs.*8; $P<0.05$, Table 2), knowing that each 1-MET increment in CRF is associated with a 13% and 15% lower risk of all-cause and cardiovascular disease mortality, respectively.[34] The need to measure CRF in clinical practice and cardiac rehabilitation programs is, therefore, highlighted, not only to characterize the health risk of the patients, but also to determine the treatment efficiency after the exercise intervention.

It is well known that $\dot{V}O_{2peak}$, VT1, and VT2 are the gold standard references for the assessment of CRF.[29] Therefore, another interesting result demonstrated by these data is that VT only improved in high-volume HIIT, but not in the low-volume HIIT group

(Table 2). This result could be justified by a superior exercise volume at intensities relative to VT in the high-volume group compared to the low-volume HIIT group (24min *vs.* 12min per week at intensities >VT2, respectively). It is likely, therefore, that a minimum necessary training load, and not only high-intensity, will be necessary to stimulate change in submaximal variables such as VT.[44]

The significant and positive changes observed in waist circumference (*i.e.,* decrease) for both HIIT groups and no changes in the AC group demonstrate: 1) the effectiveness of supervised-HIIT training to improve one of the most common indices of visceral adiposity associated with systemic inflammation and cardiovascular risk;[45] and 2) the likely need to also include a stricter diet intervention (*i.e.,* individual calorie-intake design, and not only counselling). Adding to that, we should support the Fat-but-Fit paradigm in this population, knowing that a medium-high CRF level may attenuate the adverse consequences of obesity on health.[26]

The results of this study should be interpreted within the context of its limitations. The first one consists of the relatively small sample size, not reaching "*a priori*" statistical power for the study. However, taking into account the estimated effect size with such a small sample per group we do find that our results are very promising. Second, we required AC participants to follow-up on the physical activity recommendations and to keep a daily record of their performed physical activity; however, most of them either did not record any activity, or did not comply with the recommendations.

CONCLUSIONS

This study suggests that a 16-week intervention with two days per week of different HIIT volumes with Mediet recommendations could equally improve CRF and waist circumference after an MI. Low-volume HIIT may be a potent and time-efficient exercise training strategy to induce functional capacity in this population. In clinical practice, supervised and individually designed exercise and diet by specialists should be prescribed rather than just generally recommended.

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