

Effect of interval exercise training programme on C-reactive protein in the non-pharmacological management of hypertension: a randomized controlled trial

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Abstract

Objective: Increased serum levels of inflammatory mediators have been associated with numerous disease states including hypertension. C-reactive protein (CRP) levels are associated with future development of hypertension and cardiovascular event in hypertension, which suggests that hypertension, is in part an inflammatory disorder. The objective of this study was to determine the effect of interval training programme on blood pressure and CRP in the non pharmacological management of hypertension.

Methods: Two hundred and forty five male subjects with mild to moderate (Systolic Blood Pressure [SBP] between 140-179 & Diastolic Blood Pressure [DBP] between 90-109 mmHg) essential hypertension were age-matched and randomly grouped to interval (n=140) and control groups (n=105). The interval (work: rest ratio of 1:1) groups involved in an 8-weeks interval training programs for between 45-60 minutes, at intensities of 60-79% of HR reserve, while the control group remained sedentary during this period. SBP, DBP, VO₂max and CRP were assessed. Students't and Pearson correlation tests were used in data analysis.

Results: Findings of the study revealed significant effect of interval exercise training program on SBP, DBP and CRP. The study also showed positive significant correlation between changes in CRP and changes in SBP (r=0.225) and DBP (r=0.324) at p<0.05.

Conclusions: It was concluded that moderate intensity interval training programs is effective in the non-pharmacological management of hypertension and may prevent cardiovascular event through the down regulation of CRP in hypertension.

Keywords: Hypertension; interval exercise; C-reactive protein; blood pressure.

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Résumé

Objectif: L'augmentation des taux sériques de médiateurs inflammatoires a été associée à de nombreux états pathologiques dont l'hypertension. Les protéines C-réactive (CRP) sont associées au développement futur de l'hypertension et de cas cardiovasculaires dans l'hypertension, ce qui montre que l'hypertension, est en partie un trouble inflammatoire. L'objectif de cette étude était de déterminer l'effet du programme de formation à intervalle sur la pression artérielle et sur la CRP dans la gestion non-pharmacologique de l'hypertension.

Méthodes: Deux cent quarante-cinq patients de sexe masculin de pression artérielle essentielle légère à modérée (pression artérielle systolique [PAS] entre 140-179 et la pression artérielle diastolique [PAD] entre 90-109 mmHg) ont été appariés selon l'âge et regroupés au hasard à intervalle (n = 140) et les groupes pilotes (n = 105). Les groupes intervalles (rapport travail: repos de 1:1) impliqués dans un programme de formation à intervalle de 8 semaines entre 45-60 minutes, à des intensités de 60-79% de la réserve FC, tandis que le groupe pilote est resté sédentaire pendant cette période. Le PAS, le PAD, VO₂max et la CRP ont été évaluées. Les tests de corrélation de Pearson et Students't ont été utilisés dans l'analyse des données.

Résultats: Les résultats de l'étude ont révélé l'effet significatif de l'exercice d'intervalle du programme de formation sur la PAS, PAD et la CRP. L'étude a également montré une corrélation positive considérable entre les variations des taux de CRP et l'évolution de la PAS (r = 0,225) et la PAD (r = 0,324), p < 0,05.

Conclusions: on conclut que les programmes de formation à intervalle d'intensité modérée sont efficaces dans le traitement non pharmacologique de l'hypertension et peut empêcher des cas cardiovasculaires à travers la régulation à la baisse de la CRP dans l'hypertension.

Introduction

Hypertension is a major global health problem and public-health challenge, demanding a vast proportion of health care resources directly and indirectly because of its high and increasing prevalence and the concomitant risks of cardiovascular and kidney disease, disability-adjusted life-years and mortality [1,2]. It has been reported that sedentary and unfit

normotensive have 20-50% increased risk of developing hypertension during follow up when compared with their more active and fit peers [3]. Regular aerobic physical activity adequate to achieve at least a moderate level of physical fitness has been shown to be beneficial for both preventive and treatment of hypertension [4].

The endothelium is vital to the maintenance of vascular health. It is a critical determinant of vascular tone and patency, reactivity, inflammation, vascular remodeling, and blood fluidity [1, 2]. Nitric oxide (NO) is the most potent vasodilator and is secreted by the endothelium. It is synthesized from Larginine by the endothelial enzyme NO synthase (eNOS). Increased serum levels of inflammatory mediators have been associated with numerous disease states including atherosclerosis, type II diabetes, hypertension, depression, and overall mortality [4]. C-reactive protein levels are associated with future development of hypertension, which suggests that hypertension is in part an inflammatory disorder [5]. Higher levels of C-reactive protein may increase BP by reducing nitric oxide production in endothelial cells [6-7], resulting in vasoconstriction and increased production of endothelin 1 [8, 9]. It is also apparent from studies [10-12] that CRP contributes to the development of cardiovascular event in hypertension and in fact plays an active role throughout the various steps of the inflammatory process of cardiovascular disease.

Several studies [13-15] have shown an inverse relationship between physical activity levels and biomarkers of inflammation in both healthy and hypertensive patients. However, no study has systematically and objectively determined the effect of exercise on CRP in the management of hypertension. The purpose of the present study was therefore to determine the effect of interval exercise on blood pressure and CRP in the management of hypertension.

Materials and methods

Research design

In the present study, age matched randomized double blind independent groups design was used to determine the influence of interval training program on blood pressure and CRP. Subjects' age were arranged in ascending order (50 to 70 years) and then assigned to, continuous and control groups in an alternating pattern (age matched). One week wash out period was established and pretest (fasting blood sample collection and stress test) was administered to all subjects on the last day of the wash out period. Following wash out and pretest, all subjects (interval & control) were placed on antihypertensive (methyldopa) drug. The interval group involved in

an interval training program for 8 weeks and the control group remains sedentary during this period. Following the 8 weeks of training and sedentary period, another one week wash out period was establish and posttest was administered to all subjects on the last day of the wash out period.

Subjects

Population for the study was male essential hypertensive subjects attending the hypertensive clinic of Murtala Muhammed Specialist Hospital Kano Nigeria. Subjects were fully informed about the experimental procedures, risk and protocol, after which they gave their informed consent in accordance with the American College of Sports Medicine (ACSM) guidelines, regarding the use of human subjects [16]. Ethical approval was granted by the Ethical Committee of Kano State Hospitals Management Board.

Inclusion criteria

Only those who volunteered to participate in the study were recruited. Subjects between the age range of 50-70 years with chronic mild to moderate and stable (>1 year duration) hypertension (SBP between 140-179 & DBP between 90-109 mmHg) were selected. Subjects who had stopped taking antihypertensive drugs or on a single antihypertensive medication (methyldopa) were recruited for the study. All subjects were sedentary and have no history of psychiatry or psychological disorders or abnormalities.

Exclusion criteria

Obese (BMI > 30kg/m²) or underweight (BMI < 18.5kg/m²), smokers, alcoholic, diabetic, other cardiac, renal, respiratory disease patients were excluded. Those involved in vigorous physical activities and above averagely physically fit (VO₂max >27 & >33 ml/kg.min for over 60 & 50 years old respectively) were also excluded.

A total of 323 chronic and stable, essential mild to moderate male patients with hypertension satisfied the necessary study criteria. Subjects were age-matched and randomly grouped into interval (162) and control (161) groups.

Pretest procedure

Wash out period

All subjects on anti-hypertensive drugs were asked to stop all forms of medication and in replacement, were given placebo tablets (consisted of mainly lactose and inert substance) in a blind method [17, 18]. All subjects including those not on any antihypertensive medications were placed on placebo

tablets for one week (7 days); this is known as “Wash out period”. The purpose of the wash out period was to get rid of the effects of previously taken antihypertensive drugs/medications. During the wash out period all subjects were instructed to avoid any strenuous physical activities and report to the hypertensive clinic for daily blood pressure monitoring and general observation. The pretest procedure was conducted at the last day of the wash out period, in the Department of Physiotherapy of Murtala Mohammed Specialist Hospital (MMSH), Kano between 8:00 am and 10:00 am.

Physiological measurement

Subjects resting BP (SBP and DBP) and Heart Rate (HR) were monitored from the right arm as described by Walker *et al* [19] using an automated digital electronic BP monitor (Omron digital BP monitor, Model 11 EM 403c; Tokyo Japan). The equipment was used to take the BP and HR at rest, during exercise and after exercise test. This procedure was repeated and the averages of the two readings were recorded. These measurements were monitored between 8:00 am and 10:00 am each test day.

Blood sample collection

Immediately after the post training wash out period, fasting blood samples were collected. Five ml syringe was used for blood sample collection, using the procedure described by Bachorik [20]. One milliliter of blood sample was immediately transferred into a special container containing anticoagulant (heparin, 75U/ml) for WBC count. All samples were stored in a refrigerator at -80°C until analysis [21].

C - reactive protein

The high sensitive C - reactive protein was determined qualitatively and semi-quantitatively using commercial latex agglutination method (Latex liquid reagents and manual by Dialab Produktion und Vertrieb Von Chemisch, Gesellschaft M.B.H). The procedure used is as recommended by the manufacturer.

Stress test

The Young Men Christian Association (YMCA) sub-maximal cycle ergometry test protocol was used to assess subject's aerobic (VO_2max) power as described by ACSM [22], Golding *et al.* [23]. The YMCA protocol uses two to four 3-minutes stage of continuous exercise, two HR-power output data points needed (steady state HR) of between 110 and 150 beats/min. The bicycle seat height was adjusted and the subjects' knee slightly flexed when the pedal

was in the down position. Exercise test started with a 2 to 3 minutes warm up at zero resistance in order to acquaint the subjects with the cycle ergometer. According to Brook *et al* [24]; Pollock and Wilmore [25] middle aged, less fit, cardiac patient generally begins at 100 or 150 to 300 $\text{kgm}\cdot\text{min}^{-1}$ (17w or 25w to 50w respectively) with power increments of 5-25 watts per stage. At the end of the test, a 2 to 3 minutes recovery period (cool down) at zero resistance pedaling was administered.

The two steady state HR were plotted against the respective workload on the YMCA graph sheet. A straight line was drawn through the two points and extended to the subjects predicted maximum HR (220-age). The point at which the diagonal line intersected the horizontal line predicted HR max line representing the maximal working capacity for the subject. A perpendicular line was dropped from this point to the baseline where the maximal physical workload capacity was read in $\text{kg}\cdot\text{m}\cdot\text{min}^{-1}$, which was used to predict the subjects VO_2max .

Test procedure

The test procedure was conducted in the Department of Physiotherapy of Murtala Mohammed Specialist Hospital (MMSH), Kano between 8:00 am and 10:00 am.

Training program

Following stress test and prior to the exercise training, all subjects in the control, interval and control groups were re-assessed by the physician. During the training and sedentary period (8 weeks) all subjects in the interval and control groups were placed on methyl dopa according to their pre-recruitment doses and responses at 250mg and 500mg daily. Methyl dopa was preferred because it does not alter normal hemodynamic responses to exercise [26]. It is a well-tolerated and mostly prescribed antihypertensive drug in Nigeria [27], particularly Northern Nigeria where the study was conducted and it is also useful in the treatment of mild to moderately severe hypertension [28]. Subjects maintained these prescriptions with regular medical consultation and observation throughout the period of this study.

The interval group (group 1)

After a 10-minutes warm up (pedaling at zero resistance), subjects in the interval group exercised on a bicycle ergometer at a moderate intensity of between 60-79% of their HR reserve [29-31] that was estimated as stated below, from 220 minus the age of a subject as recommended by ACSM [29]. The starting

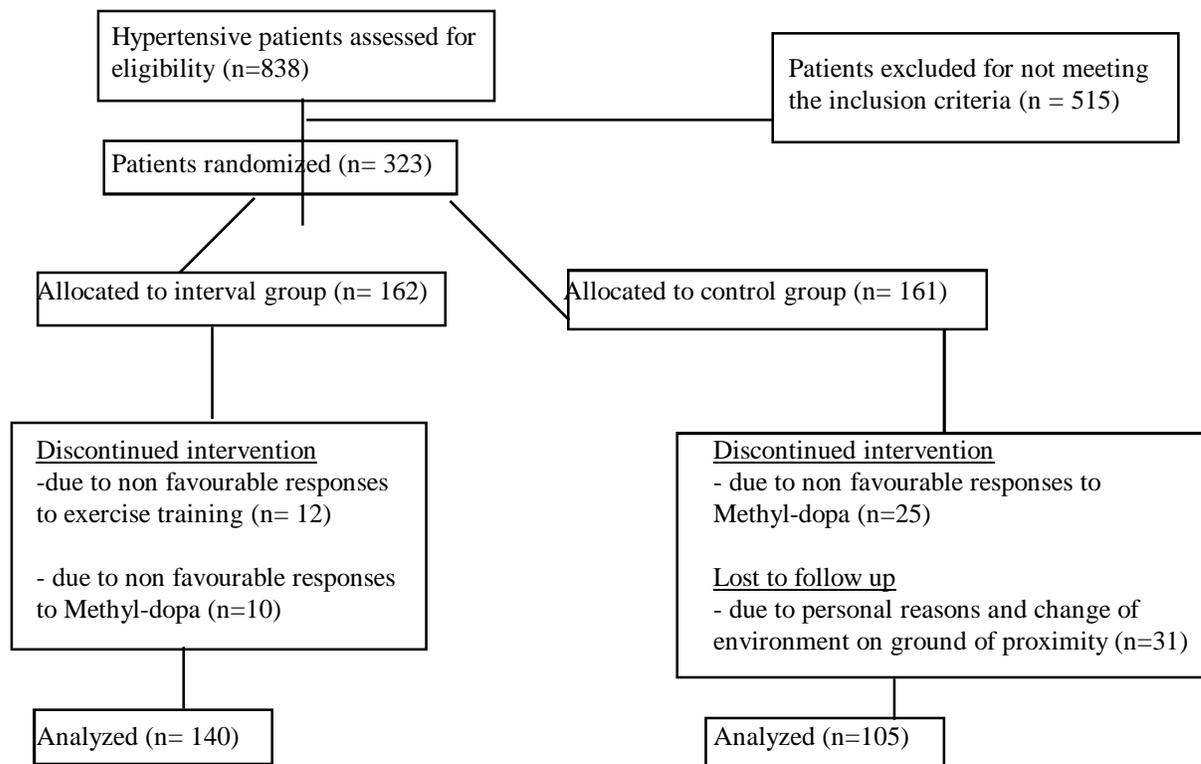


Fig. 1: Study design flow chart

workload was 100 kgm (17 watts) which was increased at a pedal speed of 50rpm to obtain 60% of their HR reserve was increased in the first two weeks to and level up at 79% of their HR reserve and this value was maintained throughout the remaining part of the training period at a work: rest duration of 1:1 of 6 minutes each [29]. During the 6-minutes rest interval period, subjects pedal at zero intensity. The initial of exercise session was increased from 45 minutes in the first two weeks of training to and leveled up at 60 minutes throughout the remaining part of the training. Following the exercise, another 10- minutes cool down was established by pedaling at zero resistance. Exercise session of three times per week was maintained throughout the 8 weeks period of training.

Estimation of the training HR

Estimated HR max = 220 – Age in years

HR reserve =HR max – HR resting

Training HR = (HR max – HR resting) x intensity percentage + HR resting

Or

HR reserve x intensity Percentage + HR resting [29]

The control group (group 3)

Subjects in the control group were instructed not to undertake any organized/structured physical activity apart from the activity of daily living during the 8 weeks period of study.

Posttest procedure

Wash out period

At the end of the 8 weeks training and sedentary period, all subjects were asked to stop methyl-dopa. Subjects were instead prescribed with placebo tablets in a blinded method for one week in order to get rid of the effect of the methyl-dopa taken during the training period.

Post training physiological (SBP and DBP) assessment and stress test were conducted as earlier described in the pretest procedures using standardized protocols, techniques and methods by the same investigators.

All pre and post test measurements were recorded on a data sheet. Two hundred and forty five subjects (140 from interval and 105 from control groups) completed the eight weeks training program. Seventy eight subjects (22 from interval and 56 from control groups) had dropped out because of non-compliance, unfavourable responses to methyl-dopa and exercise training or had incomplete data; therefore, the data of 245 subjects were used in the statistical analysis (figure 1).

Statistical analysis

Following data collection, the measured and derived variables were statistically analyzed. The descriptive statistics (Means & standard deviations) of the subjects' physical and physiological characteristics, estimated VO_2 max and CRP were determined. Student's t test and Pearson product moment

Table 1: Groups pre and posttest mean(X) \pm standard deviation (SD) (N = 245)

Variables	Interval group X \pm SD (n=140)		Control group X \pm SD (n= 105)	
	Pretest	Posttest	Pretest	Posttest
SBP(mmHg)	166.05 \pm 14.10	150.35 \pm 16.67	160.87 \pm 13.23	163.47 \pm 14.88
DBP(mmHg)	96.80 \pm 3.38	94.08 \pm 5.31	97.17 \pm 1.43	96.10 \pm 2.67
VO ₂ max(ml/kg/min)	23.67 \pm 9.15	37.46 \pm 7.42	21.23 \pm 5.76	22.82 \pm 7.44
CRP(mg/L)	0.16 \pm 0.05	0.12 \pm 0.04	0.13 \pm 0.04	0.13 \pm 0.05

Table 2: Groups changed scores mean(X) \pm standard deviation (SD) and t-test values (N = 245)

Variables	Changed score values X \pm SD		t-values	p-values
	Interval group n= 140	Control group n= 105		
SBP(mmHg)	15.70 \pm 13.16	2.60 \pm 7.85	13.148	0.000*
DBP(mmHg)	-4.72 \pm 4.34	-1.07 \pm 1.76	-6.560	0.000*
VO ₂ max(ml/kg/min)	13.79 \pm 9.99	1.59 \pm 3.52	11.959	0.000*
CRP(Mg/L)	-0.04 \pm 0.05	0.01 \pm 0.03	-8.121	0.000*

* Significant, $p < 0.05$

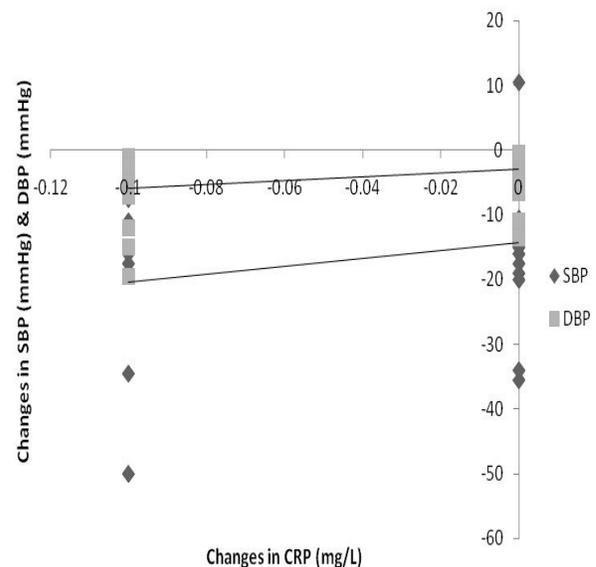
correlation tests were computed for the variables of interest. In the t and correlation tests, the difference between subjects post-training and pre-training measurements (changed score) were used as dependent measures. All statistical analysis was performed on a Toshiba compatible microcomputer using the statistical package for the social science (SPSS), (Windows Version 16.0 Chicago IL, USA). The probability level for all the above tests was set at 0.05 to indicate significance.

Results

The subject's age ranged between 50 and 70 years. Mean age, height, weight and BMI \pm SD: Interval group (58.40 \pm 6.91 years, 167.78 \pm 7.81 cm, 70.18 \pm 11.37 kg, 24.96 \pm 3.88 kg.m⁻²) and Control group (58.27 \pm 6.24 years, 167.89 \pm 5.31 cm, 68.47 \pm 17.07 kg, 24.16 \pm 4.91 kg.m⁻²). There was no significant difference in age between groups ($t=1.156$, $p=0.876$).

Subject's pre versus (Vs), post treatment mean BP \pm SD mmHg, CRP and VO₂max ml.kg⁻¹.min⁻¹ for the exercise (SBP 166.05 \pm 14.10; DBP, 96.80 \pm 3.38; CRP 0.16 \pm 0.05 & VO₂max 23.67 \pm 9.15 Vs SBP, 150.35 \pm 16.67; DBP, 94.08 \pm 5.31; CRP 0.12 \pm 0.04 & VO₂max 37.46 \pm 7.42) group and control (SBP 160.87 \pm 13.23; DBP, 97.17 \pm 1.43; CRP 0.13 \pm 0.04 & VO₂max 21.23 \pm 5.76 Vs SBP, 163.47 \pm 14.88; DBP, 96.10 \pm 2.67; CRP 0.13 \pm 0.05 & VO₂max 22.82 \pm 7.44) group (table 1).

Table 2 students' t test results indicated significant reduction in the interval group over control in SBP ($t=13.148$, $p=0.000$), DBP ($t= -6.560$, $p=0.000$), CRP ($t = -8.121$, $p= 0.000$) and VO₂ max ($t= 11.959$, $p=0.000$) at $p<0.05$. Results showed significant positive correlation between changes in CRP and SBP ($r= .225$); CRP and DBP ($r= .324$) figure 2.



SBP ($r= .225^{**}$)

DBP ($r= .324^{**}$)

**significant, $p < 0.01$

Fig. 2: Correlation between changes in CRP and Blood pressure (N=140).

Discussion

The purpose of the present study was to determine the effect of interval exercise on blood pressure and CRP in male hypertensive subjects. Results of the study indicated significant positive effect of interval exercise training on blood pressure and CRP. Results also showed significant positive correlation between changes in C-reactive protein (CRP) and changes in blood pressure (SBP and DBP) following aerobic interval exercise.

Results of the present study on the effect of exercise on blood pressure are in agreement with several previous studies [32-34]. Kullo *et al* [35] investigated the effect of aerobic exercise on CRP of patients with CHD. One hundred and seventy two asymptomatic men with CHD (age, 51±9.3years) engaged in a symptomless graded treadmill aerobic exercise. They reported a significant reduction in CRP count and inverse correlation with VO₂max ($r=-0.40$, $p=0.001$) and IL-6 ($r=-0.38$, $p=0.001$). Kohut *et al* [36] conducted a study that was in agreement with the present study, though on healthy subjects. They investigated the effect of aerobic exercise on the inflammatory mediators (CRP, IL-6, IL-16 and tumour necrosis factor [TNF]) sixty four years old adults, also sub-group of subjects treated with non selective beta(1) beta (2)adrenergic antagonist were assigned to either aerobic exercise or flexible/strength exercise treatment for 3 days /week, 45minutes for 10 months. They reported significant reduction in CRP, IL-6, TNF and IL-16 in aerobic exercise compared to flexible/strength exercise.

Hjelstuen *et al* (37) conducted another similar study in 2006, investigating the effect of physical activity on CRP of drug treated hypertensive men. The participant ($n=177$, age=40-74 years) were randomly recruited from the hypertension high-risk management trial. Subjects were overweight and sedentary. Subjects engaged in aerobic exercise on a cycle ergometer to exhaustion, they reported a significant reduction in CRP in the aerobic exercise over flexible/strength exercise at $p= 0.33$, also that CRP is inversely related to the level of physical activity.

In cross-sectional analyses, Volpatoe *et al* [38] found IL-6 levels to be inversely related to exercise tolerance in disabled older women, while Taaffe *et al* [39] reported an inverse relationship between accumulated moderate and strenuous activity with IL-6 in 880 adults aged 70-79 years. Smith *et al* [40] found that a 6 month exercise program reduced TNF- ($n=43$, average age=49.0 y). Tsukui *et al* [41] reported exercise training in 29 obese women (average

age=56 y) reduced TNF- with only modest weight loss. It is suggested that regular exercise induces suppression of TNF-alpha and thereby offers protection against TNF-alpha-induced insulin resistance. Recently, IL-6 was introduced as the first myokine, defined as a cytokine, which is produced and released by contracting skeletal muscle fibres, exerting its effects in other organs of the body. Myokines may be involved in mediating the beneficial health effects against chronic diseases associated with low-grade inflammation such as diabetes and cardiovascular diseases.

It is generally at large accepted that the physiological mediator of low grade chronic inflammation and raised CRP is the TNF-alpha, which has been proven to be down-regulated by regular physical activities. Another mechanism is that the post exercise hypotension which is accompanied by a decrease in serum catecholamines, norepinephrine, dopamine, cortisol, sympathetic nervous system, plasma rennin activity [42-44], thus suppressing inflammatory reaction and finally down-regulating CRP concentration.

Conclusion and clinical application

The present study demonstrated a rationale basis for the adjunct role of moderate intensity interval exercise training in the down regulation of CRP and blood pressure. CRP a marker of inflammatory reaction could also be a major cardiovascular event risk factor in hypertension. Therefore, exercise specialists and other therapists should feel confident in the use of this form of therapy as non-pharmacological adjunct management and control of hypertension.

Limitation of the study

The present study demonstrated a rationale bases for the role of interval exercise training in the down regulation of the blood pressure and CRP. However, the limitation of the study includes lack of long time follow up; this limitations warrant attention in future studies.

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