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Modulatory Effect of Inflammation on Blood Pressure Reduction via Therapeutic Lifestyle Change

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ABSTRACT

Purpose: Since inflammatory status, as determined by C-reactive protein (CRP) levels, is correlated with many cardiovascular (CV) disease risk factors and major CV events, we sought to determine if median levels of CRP can modulate blood pressure changes as well as other CV risk factors that are typically improved by therapeutic lifestyle changes with formal cardiac rehabilitation and exercise training (CRET) programs.

Methods: We retrospectively evaluated CRP status and standard CV risk factors both before and after formal, phase II CRET programs (12 weeks; 36 educational and exercise sessions) in 635 consecutive patients with coronary artery disease after major CV events.

Results: The median CRP level at baseline was 3.2 mg/L (range, 0.2–80.1 mg/L; mean, 5.8±8.4 mg/L). After CRET, both the patients with high and those with low CRP concentrations exhibited statistically significant improvements in most CV risk factors when their CRP levels were divided by median levels. However, systolic, diastolic, and mean arterial blood pressure improved in patients with low CRP levels (each by −4%) but did not change significantly in patients with high CRP levels. In multiple regression models, only young age, low CRP levels, and low body mass index were significant independent predictors of improved mean arterial blood pressure after CRET.

Conclusions: In contrast to patients with coronary artery disease and low levels of CRP, patients with high baseline CRP levels did not demonstrate significant reductions in blood pressure after therapeutic lifestyle changes via formal CRET programs.

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INTRODUCTION

Prospective studies[1–6] have demonstrated that plasma levels of C-reactive protein (CRP) are a strong independent predictor of future vascular events among individuals with and without known cardiovascular disease, and elevated levels of CRP have been positively correlated with most cardiovascular risk factors. Inflammation has recently been hypothesized to play a contributory role in the development of hypertension, and elevated CRP levels have been associated with elevated blood pressure (BP) levels in cross-sectional studies.[7,8] Higher CRP levels may increase BP by reducing nitric oxide production in endothelial cells, resulting in vasoconstriction and increased endothelin 1 production, as well as by upregulating angiotensin type 1 receptor expression.[9–11] Recently, elevation of CRP levels has been shown to increase the risk for the future development of hypertension, suggesting that hypertension is in part a disorder of inflammation.[12] We are not aware, however, of any studies investigating the role of inflammation in modulating efficacy of therapies designed to reduce BP.

Cardiac rehabilitation and exercise training (CRET) is a proven modality for reducing the overall burden of cardiovascular risk and has been shown to significantly improve major cardiac risk factors, including exercise capacity, percentage of body fat, BP, and lipids.[13,14] Moreover, we have recently reported[14,15] the effectiveness of CRET in reducing both the prevalence of metabolic syndrome and CRP, whose levels can be diminished by as much as 40% to 50%.

We sought to determine if inflammatory status can modulate BP changes, as well as other risk factors typically improved with therapeutic lifestyle change, by using CRET.

METHODS

We retrospectively evaluated CRP status in 635 consecutive patients with coronary artery disease (74% percutaneous intervention, 18% bypass sur-

gery, and 29% myocardial infarction) enrolled in and completing a 3-month formal program of CRET and measured relevant hemodynamic, anthropometric, lipid, and clinical data at baseline and upon program completion. Detailed program components have been reviewed elsewhere,[13,16] but in brief, patients received both individual and group counseling from a registered dietitian in dietary management as recommended by the Adult Treatment Panel III guidelines,[17] with special emphasis on the Mediterranean diet[18] and a sodium-restricted diet in patients with hypertension.[19] In overweight patients, modifications in the diet plan were introduced to promote weight loss. Patients received formalized exercise instruction and met 3 times per week for group exercise classes and were encouraged to exercise on their own (1–3 times per week) in between sessions. Patients' exercise recommendations were tailored toward the anaerobic threshold achieved during entry testing. Specific weight management guidance was given to overweight and obese subjects. Educational classes were given with regard to all aspects of risk for coronary artery disease, including hypertension, smoking cessation, and diabetes management.

Fasting lipid, glucose, and CRP levels; percentage of body fat; abdominal girth; and resting BP were obtained prospectively upon entry and completion of the formal rehabilitation program. Most subjects entered the program between 3 to 5 weeks following hospital discharge (mean, 3.6±3.5 weeks). BP was measured in the morning, at rest, with the patient sitting, with the use of a manual cuff. High-sensitivity assays for CRP were performed according to methods described by the manufacturer (Dade Behring Inc, Deerfield, IL).[20] The percentage of body fat was determined by the skinfold technique by using the average of 3 skinfolds (thigh, chest, and abdomen in men; thigh, triceps, and suprailium in women).[21,22] All measurements were made in the early morning before exercise.

Patients who were taking antihypertensive medication (61%), lipid-lowering medication (65%) including statins, or hormone replacement therapy received constant doses for a period of at least 6 weeks before the initial assessment and throughout the evaluation period.

Means or proportions for baseline risk factors were computed for all subjects, and the significance of any differences in means was tested with the Student *t* test; differences in proportions were tested with the χ^2 statistic. Because the distributions of CRP levels are rightward skewed, median concentrations were computed for this parameter and the significance of any differences was assessed using the Wilcoxon rank sum test. Statistical analysis using paired and unpaired *t* tests was performed with Statview 5.0.1 (SAS Institute Inc, Cary, NC). A *P* value of ≤0.05 was considered statistically significant, and variability is reported by using standard deviation.

Table 1. Baseline Characteristics of the Study Cohort (N=635)

Characteristic	Value
Age, y	65±11
Women, %	28
Total cholesterol, mg/dL	170±36
HDL-C, mg/dL	42±13
LDL-C, mg/dL	100±36
Triglycerides, mg/dL	154±92
Glucose, mg/dL	108±25
Mean CRP, mg/L	5.8±8.4
Median CRP, mg/L	3.2
BMI, kg/m^2	28.3±5
Body fat, %	28.9±7.6
Systolic BP, mm Hg	137±19
Diastolic BP, mm Hg	75±13
Mean arterial pressure, mm Hg	96±13
Peak VO_2, mL/kg/min	16.2±4.8
Antihypertensive medications, %	61
Lipid-lowering medications, %	65

HDL-C indicates high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CRP, C-reactive protein (high-sensitivity assay); BMI, body mass index; BP, blood pressure; and peak VO_2, peak oxygen uptake.

RESULTS

Baseline data for the 635 patients enrolled in the rehabilitation program are detailed in Table 1. In our rehabilitation cohort, 179 patients (28%) were women (33% were receiving hormone replacement therapy), and the mean age of our cohort was 65±11 years. The mean body mass index (BMI) of the cohort was 28.3±5 kg/m^2, and the mean percentage of body fat was 28.9±7.6%. Of note, 41% of subjects upon entry were classified as overweight (25 kg/m^2≤BMI<30 kg/m^2), and an additional 32% were classified as obese (BMI≥30 kg/m^2). The median concentration of CRP at entry was 3.2 mg/L (range, 0.2 to 80.1 mg/L); mean concentration was 5.8±8.4 mg/L at baseline. A total of 394 patients (62%) were receiving statin therapy, and 388 patients (61%) were receiving antihypertensive therapy upon entry and during the 3-month rehabilitation program. At entry, CRP levels were weakly, but significantly, correlated to BMI (r=0.09; *P*=0.04), resting heart rate (r=0.12, *P*=0.02), systolic BP (r=−0.12, *P*=0.005), diastolic BP (r=−0.13, *P*=0.002), and mean arterial pressure (r=−0.14, *P*=0.0006).

Table 2. Baseline Differences Between Subjects With High and Low C-Reactive Protein Levels

	High CRP (>3.2 mg/L) (n=317)	Low CRP (≤3.2 mg/L) (n=318)	*P*
Age, y	65±10	65±11	NS
Women, %	33	21	0.002
Total cholesterol, mg/dL	172±35	170±34	NS
HDL-C, mg/dL	41±14	42±14	NS
LDL-C, mg/dL	99±29	99±27	NS
Triglycerides, mg/dL	165±96	146±92	0.07
Glucose, mg/dL	108±25	107±23	NS
Mean CRP, mg/L	10±10	1.5±0.8	<0.0001
Median CRP, mg/L	6.6	1.3	<0.0001
BMI, kg/m^2	28.8±5.2	27.8±4.7	0.02
Body fat, %	29.7±7.8	28.1±7.6	0.01
Systolic BP, mm Hg	136±19	139±20	NS
Diastolic BP, mm Hg	74±12	76±14	NS
Mean arterial pressure, mm Hg	95±12	97±14	NS
Peak VO_2, mL/kg/min	15.5±4.3	17.1±5.2	<0.0001
Resting heart rate, bpm	69±12	65±13	0.004

HDL-C indicates high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CRP, C-reactive protein (high-sensitivity assay); BMI indicates body mass index; BP, blood pressure; peak VO_2, peak oxygen uptake; and NS, not significant.

Patients were divided into 2 groups based on baseline median CRP concentrations. Baseline differences between groups with high (>3.2 mg/L) and low (≤3.2 mg/L) CRP levels are described in Table 2. Compared to patients with low CRP levels, patients with elevated CRP levels were more likely to be women (33% vs 21%, $P=0.002$) and had higher triglyceride concentrations (165±96 vs 146±92 mg/dL, $P=0.07$), higher BMI (28.8±5.2 vs 27.8±4.7 kg/m^2, $P=0.02$), higher percentage of body fat (29.7±7.8 vs 28.1±7.6%, $P=0.01$), higher resting heart rate (69±12 vs 65±13 bpm, $P=0.004$), and lower peak VO_2 (15.5±4.3 vs 17.1±5.2 mL/kg/min, $P<0.0001$).

Following CRET, both the groups with high and those with low CRP levels exhibited statistically significant improvements in percentage of body fat (−3% and −4%, respectively), HDL cholesterol levels (+7% and +7%, respectively), triglyceride levels (−12% and −8%, respectively), peak V_{O_2} (+11% and +9%, respectively), and resting heart rate (−6% and −6%, respectively) (Tables 3 and 4). Systolic, diastolic, and mean arterial pressure statistically improved (each by −4%) in patients with low CRP levels but did not change in patients with high CRP levels. In a multiple regression model incorporating 9 independent baseline variables (age, gender, BMI, percentage of body fat, peak VO_2, HDL cholesterol, LDL cholesterol, triglycerides, and CRP), only age, CRP levels, and BMI were significant independent predictors of reduction in mean arterial pressure (Table 5).

DISCUSSION

The major finding of this study is that, in contrast to patients with coronary artery disease who have low levels of CRP, patients with high baseline CRP levels do not demonstrate BP reduction after therapeutic lifestyle change via CRET.

Table 3. Effects of Cardiac Rehabilitation and Exercise Training in Patients With High C-Reactive Protein Levels (>3.2 mg/L) (n=317)

	Before	After	% Change	*P*
Total cholesterol, mg/dL	172±35	174±36	1	NS
HDL-C, mg/dL	41±14	44±13	7	<0.0001
LDL-C, mg/dL	99±29	102±36	3	NS
Triglycerides, mg/dL	165±96	145±76	−12	0.005
Glucose, mg/dL	108±25	106±24	−2	NS
Median CRP, mg/L	6.6	3.5	−47	<0.0001
Mean CRP, mg/L	10±10	5.3±6.2	−47	<0.0001
$P_{EAK}VO_2$, mL/kg/min	15.5±4.3	17.2±5.9	11	<0.0001
Resting heart rate, bpm	69±12	65±12	−6	0.0002
BMI, kg/m^2	28.8±5.2	28.8±5.1	–	NS
Body fat, %	29.7±7.8	28.8±8	−3	<0.0001
Systolic BP, mm Hg	136±19	136±18	–	NS
Diastolic BP, mm Hg	74±12	74±13	–	NS
Mean arterial pressure, mm Hg	95±12	95±12	–	NS

HDL-C indicates high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CRP, C-reactive protein (high-sensitivity assay); peak VO_2, peak oxygen uptake; BMI, body mass index; BP, blood pressure; and NS, not significant.

Table 4. Effects of Cardiac Rehabilitation and Exercise Training in Patients With Low C-Reactive Protein Levels (≤3.2 mg/L) (n=318)

	Before	After	% Change	*P*
Total cholesterol, mg/dL	170±34	176±37	4	0.02
HDL-C, mg/dL	42±14	45±14	7	<0.0001
LDL-C, mg/dL	99±27	103±28	4	NS
Triglycerides, mg/dL	146±92	134±80	−8	0.09
Glucose, mg/dL	107±23	111±33	4	0.09
Median CRP, mg/L	1.3	1.1	−15	NS
Mean CRP, mg/L	1.5±0.8	1.6±1.7	7	0.08
PeakVO_2, mL/kg/min	17.1±5.2	18.6±5.9	9	<0.0001
Resting heart rate, bpm	65±13	61±13	−6	<0.0001
BMI, kg/m^2	27.8±4.7	27.5±4.2	−1	0.02
Body fat, %	28.1±7.6	26.9±6.6	−4	0.0003
Systolic BP, mm Hg	139±20	134±19	−4	<0.0001
Diastolic BP, mm Hg	76±14	73±13	−4	0.005
Mean arterial pressure, mm Hg	97±14	93±13	−4	<0.0001

HDL-C indicates high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CRP, C-reactive protein (high-sensitivity assay); peak VO_2, peak oxygen uptake; BMI, body mass index; BP, blood pressure; and NS, not significant.

Inflammatory processes are now recognized as playing a fundamental role in atherogenesis.[5,23] Prospective studies[1–6] have demonstrated that plasma levels of CRP are a strong independent predictor of risk of future vascular events among individuals with and without known cardiovascular disease, and elevated levels of CRP have been positively correlated with most cardiovascular risk factors. Hypertension remains a central risk factor for cardiovascular events, and inflammation has recently been hypothesized to play a contributory role in the development of hypertension; moreover, increased CRP levels have been associated with elevated BP levels in cross-sectional studies.[7,8] Higher CRP levels may increase BP by reducing nitric oxide production in endothelial cells, resulting in vasoconstriction and increased endothelin 1 production, as well as by upregulating angiotensin type 1 receptor expression.[9–11] Recently, elevation of CRP levels has been shown to increase the risk for the development of hypertension, suggesting that hypertension is in part a disorder of inflammation.[12]

Table 5. Multivariate Analysis of Independent Predictors of Mean Arterial Blood Pressure Reduction

Variable	χ^2 Statistic	*P* Value
Age	8.6	0.003
CRP	8.5	0.004
Body mass index	4.8	0.03

CRP indicates C-reactive protein.

Moreover, elevated BP may promote vascular inflammation by alterations of pulsatile blood flow. Cyclic strain has been shown to increase soluble intercellular adhesion molecule-1 and vascular cellular adhesion molecule-1 expression by endothelial cells[24] and to upregulate endothelial cell secretion of monocyte chemoattractant protein-1,[25–27] all of which lead to increased monocyte adhesion to the endothelium.[28] Levels of CRP have been shown to correlate with mononuclear cell oxidative stress.[29] These changes, taken together, suggest that hypertension may provide multiple pathways for proinflammatory stimuli at the vessel wall.

Therapeutic lifestyle change by incorporating dietary changes, exercise training, and weight reduction has been shown to be effective in reducing BP, particularly systolic BP.[13,19,30–32] These lifestyle changes are routinely incorporated in CRET and favorable changes in lipids, BP, weight, and exercise capacity are commonly observed.[13,14] We previously reported the effectiveness of these therapies in reducing CRP,[15] suggesting that inflammation can be effectively treated nonpharmacologically. The observation that inflammation can influence efficacy of these therapies has heretofore not been reported.

In our cohort of patients with coronary artery disease, those with higher CRP values were preponderantly women, had high obesity indices, and had a reduced aerobic capacity. Although there were differences in resting pulse rate, there were no differences in BP values between groups with high and low CRP levels. Those patients with elevated

CRP concentrations had numerous cardiac benefits after rehabilitation, including improvements in HDL cholesterol, triglyceride, and CRP levels and in exercise capacity, resting pulse, and percentage of body fat. The observation of a lack of reduction in BP despite these positive effects will require further study.

There are several limitations to this study. First, this is a single-center, retrospective analysis of patients enrolled in CRET, and several confounding factors may contribute to the observations reported. Second, BP was determined by a single resting measurement, not as an average of several measurements over time. Finally, although therapeutic lifestyle changes such as CRET produce BP reductions in both hypertensive and normotensive patients, we did not stratify patients on the basis of BP status. Despite this, a multivariate analysis controlling for many confounding factors revealed that CRP status plays a significant role in effecting change in BP.

In conclusion, we have observed that inflammatory status may play a role in effecting BP reduction after therapeutic lifestyle change. Further research is needed to evaluate this effect prospectively in patients receiving pharmacologic and nonpharmacological therapy for hypertension.

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