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Effect of Meditation on Endothelial Function in Black Americans with Metabolic Syndrome: A Randomized Trial

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Abstract

Objectives—Psychological stress may play a role in metabolic syndrome. A consequence of metabolic syndrome is endothelial dysfunction, which is also influenced by psychological stress. We sought to compare the effect of consciously resting meditation (CRM), a sound (mantra)-based meditation, with a control intervention of health education (HE) on endothelial function in the setting of metabolic syndrome.

Methods—Sixty-eight black Americans with metabolic system risk factors (age 30 to 65 years) were randomized to either CRM (N=33), or to HE (N=35); interventions were matched for frequency and duration of sessions and lasted 12 months. Endothelial function was assessed by brachial artery flow-mediated dilation (FMD%) at baseline, 6 and 12 months. Arterial elasticity, metabolic risk factors, psychosocial and behavioral variables were secondary endpoints.

Results—Although FMD % improved in the CRM group over 12 months, this increase was not significantly higher than in the HE group (p=0.51 for the interaction between group and time). Non-endothelium dependent dilation and arterial elasticity did not change in either group. Most metabolic syndrome risk factors showed beneficial trends in the CRM group only. A risk factor score counting the number of metabolic syndrome components decreased in the CRM group but not in the control HE group (p=0.049 for the interaction between treatment group and time).

Conclusions—Among black Americans with metabolic syndrome risk factors, CRM, a sound-based meditation, did not improve endothelial function significantly more than a control

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intervention of health education. CRM resulted in favorable trends in metabolic syndrome risk factors which were examined as secondary outcomes.

Keywords

Endothelium; stress; metabolic syndrome; obesity

Introduction

Cardiovascular disease (CVD) and its complications carry a significantly higher morbidity and mortality in black Americans compared with white Americans. One factor likely to play a role is obesity, which is more prevalent in black Americans and is associated with insulin resistance and other cardiometabolic risk factors including elevated blood pressure (BP), elevated fasting glucose and dyslipidemia.(1,2) It is anticipated that the explosive epidemic of obesity, which is particularly a problem in the Southeast region of the nation, will trigger an increase in CVD, as already observed for hypertension (2) and type 2 diabetes.(3) These trends herald a further widening of the gap in black-white differences in CVD morbidity and mortality.

Although the etiology of insulin resistance is complex, psychological stress may play a role through increasing inflammation and other metabolic and hormonal abnormalities.(4) A major consequence of insulin resistance is endothelial dysfunction,(5) an early marker of CVD which is also influenced by psychological stress.(6-8) Insulin resistance is thought to affect endothelial function through impaired endothelial nitric oxide synthase activity caused by excess superoxide anion formation in vascular endothelial cells.(9,10)

Previous controlled clinical studies have suggested that mind-body interventions for stress reduction using a variety of meditation techniques may reduce psychological stress and improve CVD risk factors in blacks and whites, although results are heterogeneous.(11) Of various meditation techniques, transcendental meditation (TM)(12-15) and breathing awareness meditation (16-18) have been widely used in studies of black Americans and show promise in reducing BP in this population. In addition to elevated BP, it is possible that meditation approaches are beneficial in reducing other adverse consequences of obesity and metabolic syndrome, including endothelial dysfunction, inflammation and insulin resistance. These effects, however, have never been evaluated in community-dwelling blacks. We therefore conducted a randomized controlled trial among black Americans with metabolic syndrome risk factors to test the hypothesis that consciously resting meditation (CRM), a novel sound (mantra)-based meditation, improves vascular function and metabolic risk profile in participants with metabolic syndrome risk factors compared with a control arm of health education (HE) matched for frequency and duration of sessions. The primary outcome was endothelial function measured by flow-mediated dilation (FMD) of the brachial artery using ultrasound. Secondary outcomes included measures of arterial elasticity, metabolic syndrome risk factors, psychosocial and behavioral measures (symptoms of anxiety, depression, perceived stress, anger, and hostility, and physical activity), and inflammatory and metabolic biomarkers.

Methods

Study Design

This trial was part of the “Emory-Morehouse Partnership to Reduce CV Disparities” (U01HL079214), also known as META-Health. The overall goal of this research program was to characterize potential racial/ethnic differences in obesity-related cardiovascular risk. The present study was a single-site, parallel-group randomized controlled trial. The trial was

technically single-blinded given that patients were aware of which intervention they were assigned to (CRM or HE). However, participants were masked to the research hypothesis and both interventions were presented to participants as health promoting; this design should minimize expectation bias.(11) Investigators and the staff collecting the data were blinded to the treatment status of the participants. The two treatment providers were not involved with participant recruitment, data collection, analysis or interpretation. The study was approved by the Emory University and Morehouse University institutional review committees. Informed consent was obtained from all participants.

Selection of Participants

Participants were recruited from the community in metropolitan Atlanta through flyers and at health fairs, churches, university campuses and other community locations, as well as through direct referrals. They were included in the trial if they were between the ages of 30 and 65, self-identified as blacks, and met specific criteria for metabolic syndrome. According to current ATP III guidelines,(19) metabolic syndrome is defined as having at least 3 out of 5 of the following criteria: abdominal obesity (waist circumference >102 cm in men and >88 cm in women); triglycerides ≥150 mg/dL; HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women; BP≥130/≥85 mm Hg; and fasting glucose ≥100 mg/dL. However, these criteria have not been extensively validated in the black population. A paradoxical observation is that black Americans meet the metabolic syndrome criteria less often than whites despite a higher prevalence of obesity, hypertension and insulin resistance,(20) partly because of a lower triglycerides/HDL ratio.(21,22) Thus, there is concern that current metabolic syndrome definitions may underestimate risk in black Americans.(23,24) Based on this, in addition to the standard definition above, participants were eligible if they met a modified definition which did not include the lipid criteria, but they met 2 out of the following 3 criteria: abdominal obesity (waist circumference >102 cm in men and >88 cm in women); BP≥130/≥85 mm Hg; and fasting glucose ≥100 mg/dL. Subjects were excluded if they had known CVD or renovascular disease; if they had uncontrolled hypertension (systolic BP>160 mm Hg on two or more occasions or diastolic BP>105 mm Hg); if they were current smokers or had been taking over the counter vitamins such as vitamin A, C or E within three days of study initiation (since these can affect endothelial function assessments); if they were pregnant; and if they had documented history of alcohol or drug abuse or other psychiatric or medical diagnoses that would interfere with ability to attend training sessions and clinic visits for one year.

Study Protocol

After pre-screening for eligibility over the phone, potential participants attended a screening visit (Visit 1). After signing the informed consent, research staff obtained fasting blood, BP measurements and anthropometric data in order to verify the inclusion criteria. Qualifying participants were then invited to a baseline visit (Visit 2) within 2 weeks, where a number of measures were obtained, including vascular function testing, BP, anthropometry and study questionnaires. After completion of baseline assessments, participants were randomized to one of two treatment groups by blocked randomization with stratification on gender. The random allocation sequence was provided in sealed envelopes by the study statistician (who had no contact with participants) to a staff member not involved in data collection. Patients were randomized in subsequent cohorts of participants, with a minimum of 10 and a maximum of 20 in each randomization cohort (yielding no more than 10 participants per group who would start the program at any one time), for a total of 5 cohorts. All outcome data were collected in a blinded fashion with respect to the participants' treatment status. Follow-up visits for outcome assessments were performed at 6 months (Visit 3) and 12 months (Visit 4) after baseline. Three BP measurements were obtained at each visit.(25) Anthropometric measures, including height, weight, and waist circumference were measured

and fasting blood was also drawn for lab assessments. Visit 1 through 4 took place in the Cardiovascular Research Unit at the Emory University Hospital. Participant recruitment started on June 7, 2007, and the follow-up of the last randomized cohort ended on January 11, 2010.

Interventions

Both interventions were administered in the National Center for Primary Care at Morehouse School of Medicine, by providers not involved with participant recruitment, data collection, analysis or interpretation, CRM is a sound or mantra based meditation. This meditation approach was chosen because of its standardized protocol and its similarity to the TM program, which has been previously successfully implemented in black American samples. Both TM and CRM use sounds that have no meaning, but their quieting effects have been known for thousands of years. These sounds, when used properly, settle the mind and body down to a state of restful alertness. As with many TM studies, the CRM program included 21 sessions over a one year intervention period where participants learned the technique of consciously resting their mind and body. The core instruction involves a four-step course over four consecutive days (sessions 1-4) and a follow-up program over 12 months (sessions 5-21). Most sessions last 1 to 1.5 hours, and the general format is group meditation plus a lecture/discussion or videotape. In contrast to TM, CRM does not include a private Sanskrit ceremony, which has been a major objection for inner-city meditation projects. Additionally, in contrast to TM, CRM can be taught in groups, is less time consuming for participants, and is potentially more affordable, making it more accessible and easier to disseminate among minority groups. All sessions were taught by the same experienced teacher (KK). Subjects were instructed to practice CRM twice a day for 20 minutes. Participants were also given the same health education reading materials given to the control group.

Subjects randomized to HE attended the same number, size and frequency of group meetings lead by a professional health educator (LB). The program included information on prevention of CVD through lifestyle modification and was modeled on educational material disseminated by the American Heart Association (www.americanheart.org). Topics included the value of a healthy diet, exercise, and weight management. The impact of stress was discussed as it relates to weight management and physical exercise. However, to avoid contamination in the experimental design, the HE sessions did not include instructions on stress reduction or relaxation techniques. To match the 20-minute twice-a-day CRM practice, participants were instructed to undertake a 20-minute twice-a-day home practice session applying the recommendations given in this course—diet, exercise, or other lifestyle habits.

Primary Outcome

Endothelium-Dependent Flow-Mediated Vasodilation (FMD) of the brachial artery was the primary outcome of the trial. It was measured according to established methodology (26) by using an Acuson 10 mHz linear array transducer and an Acuson Aspen ultrasound system. We imaged the participants after they had rested in supine position for at least 10 minutes in a quiet setting. Optimal brachial artery images were obtained 2-10 cm above the antecubital crease. This location was marked, and all subsequent images were obtained at the same location. After baseline measurements, a BP cuff was inflated to 200 mm Hg over the proximal portion of the right arm for 5 minutes. Endothelium-dependent function was determined during the first two minutes of release of the cuff. The flow dependent response was then allowed to return to baseline over a period of five minutes.

Four triggered events (defined as the end of the T wave on the ECG) were recorded. Each triggered event consisted of three sequential frames, for a total of 12 images. These were

subsequently downloaded to an analysis system that allows automatic edge detection of the M-line that defines the intima-media interface for both the near wall and the far wall of the artery using customized software (Medical Imaging Applications Inc, Iowa). Measurements from the 12 frames were averaged. In our laboratory, the mean difference and standard deviation (SD) in FMD between assessments performed in 11 participants on consecutive days was 1.26% (SD 0.76%), with a correlation coefficient of 0.75. The mean difference and SD in the FMD between 2 readings of the same11 measurements was 0.82% (SD 0.48%) (r=0.97).

Secondary Outcomes

Endothelium-independent nitroglycerin-mediated vasodilation (NMD) and arterial stiffness were secondary vascular outcomes. NMD was evaluated as a control condition for FMD 3 minutes after administration of 0.4 mg of nitroglycerin sublingually. Data acquisition was done in a similar manner. The end point of measurement was the percent change in diameter in response to endothelium-independent nitroglycerin-mediated vasodilation (NMD%).

Arterial stiffness was assessed by means of pulse wave velocity and radial pulse wave analysis using the SphygmoCor® Pulse Wave Velocity system (PWV Medical, NSW, Australia). Peripheral pressure waveforms were recorded from the radial artery at the wrist using applanation tonometry with a high-fidelity micromanometer. After 20 sequential waveforms were acquired, a validated generalized transfer function was used to generate the corresponding central aortic pressure waveform.(27) Pulse wave velocity (PWV) was calculated as the velocity of the BP waveform between carotid and femoral arteries. Transcutaneous Doppler flow velocity recordings were carried out simultaneously at the base of the neck over the common carotid artery and at the femoral artery in the groin, and the time delay (t) as well as the distance (d) traveled by the pulse wave were measured between the two recording sites using established methods.(27) PWV was calculated as PWV=d/t. Additionally, we obtained the augmentation index (AI) from pulse wave analysis. The merging point of the incident and the reflected wave (the inflection point) was identified on the aortic pressure waveform. The AI is defined as the augmented pressure (the maximum systolic pressure minus the pressure at the inflection point) divided by pulse pressure and expressed as a percentage. Larger values of AI indicate increased wave reflection from the periphery or earlier return of the reflected wave as a result of increased pulse wave velocity, an indication of increased arterial stiffness. Reproducibility studies in our laboratory on consecutive days have demonstrated a coefficient of variation of 20.3% and 3.8% for AI and PWV, respectively.

Psychosocial and behavioral factors were measured as secondary outcomes and included psychosocial stress, measured by means of the Cohen's Perceived Stress Scale,(28) hostility, by means of the Cook-Medley Hostility Inventory,(29) anger, using the Spielberger's Anger Expression Inventory,(30) anxiety, using the Spielberger's State-Trait Anxiety Inventory, (31) depressive symptoms using the Beck II Depression Inventory (BDI), (32) including two subscales of the BDI meant to capture two distinct dimensions of depression, the cognitive/ affective subscale and the somatic subscale.(33) Physical activity was measured using the CAPS Typical Week Physical Activity Survey (CAPS-TWPAS), a 28-item questionnaire that has been validated in diverse ethnic populations.(34) This instrument provides total time spent in light physical activity (< 3 METs), moderate physical activity (3-6 METs), and vigorous physical activity (> 6 METs) in a typical week.(34) In our analysis, we focused on moderate and vigorous physical activity; because these were highly skewed, log transformation was performed prior to analysis. Compliance with the interventions was measured by class attendance as indicated by signed attendance sheets.

Metabolic profile

As additional secondary outcomes, we assessed changes in levels of **metabolic syndrome risk factors,** including abdominal obesity, fasting plasma lipids (triglycerides and HDL-cholesterol), BP, and fasting plasma glucose. We also computed a score counting the number of metabolic syndrome risk factors meeting the criteria for metabolic syndrome definition at baseline and at each of the follow-up visits. Additionally, we assessed changes in **metabolic and inflammatory biomarkers,** including leptin, adiponectin, C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor 1 (TNF-α) and plasminogen activator inhibitor 1 (PAI-1). Blood was drawn after an overnight fast. We measured CRP levels were quantified using the Dade-Behring Nephelometry System – BNII. All the other biomarkers were measured using the Fluorokine® MultiAnalyte Profiling Human Obesity Base Kit Kits from R&D Systems (Minneapolis, USA) on a Luminex 200 Bio-Plex platform (Bio-Rad, CA USA). The biomarker assays were done in the Division of Hereditary Blood Disorders at the Centers for Disease Control and Prevention.

Statistical Analysis

Data were analyzed following the intention-to-treat principle, i.e. all available data were analyzed on randomized participants (n=68), irrespective of whether they received the intervention, or completed the study.(35) All outcomes (FMD and secondary outcome measures) were analyzed as continuous variables using repeated measures mixed effects models (36) with treatment group, time point, and other study factors treated as fixed effects. The model-based means are unbiased with unbalanced and missing data, so long as the missing data are non-informative (missing at random).(37) Physical activity scores and biomarker data (CRP, IL-6, adiponectin and PAI-1) were log transformed for analysis when distribution deviated significantly from normality. Because of the lack of preliminary data on the effect of meditation on FMD at the time the study was conceived, we based our sample size on an estimated effect of 3% absolute increase in flow due to CRM, compared with HE, a standard deviation for FMD in middle-aged individuals of 3.7%, an alpha of 0.05 (2-tailed), a beta of 0.80, and an attrition rate of 20%. On the basis of these estimates, 30 participants per group were needed to show a significant difference in FMD between the two groups.

Results

Of 105 potentially eligible participants as determined through phone prescreening, 92 attended the screening visit to assess eligibility. As shown in Figure 1, of these 92 patients 68 were randomized to either CRM (n=33) or HE (n=35). Of the randomized patients, 21 and 23participants in the CRM and HE groups, respectively, attended the 6-month visit and 19 in each group attended the 12-month visit. There was no significant difference in drop-out rate between the two randomized groups. There were also no significant differences in any baseline measures comparing participants who dropped out with those who did not drop out. Compliance, assessed by class attendance averaged throughout the 12 months (21 sessions) was also similar: 50% in the CRM group and 51% in the HE group. No adverse events due to the intervention were reported.

Most participants (82%) were obese (BMI ≥30). Table 1 shows baseline characteristics of the participants by randomization group. The sample was middle-aged and predominantly female. Subjects in the CRM group had higher triglyceride levels (138 ± 81 mg/dLvs. 103 ± 50 mg/dL). There were no significant differences in other baseline factors.

Flow-Mediated Vasodilation and Other Vascular Outcomes

At baseline, there was no significant difference in mean FMD % between the CRM and the HE group (3.9%, SD 2.4%, vs. 5.1%,SD 4.2%, p=0.18). FMD % significantly improved in the CRM group over the 12-month intervention (mean change 2.1%, 95% confidence interval (CI), 0.5 to 3.7%, p=0.009), but less so in the HE group (mean change 1.4%, 95% CI, -0.2 to 2.9%, p=0.094) (Table 2 and Figure 2). The interaction between group and time, however, was not significant (p=0.51), denoting no significant difference in FMD change over time between the two groups. Non-endothelium dependent dilation (% NMD) did not change in either group and arterial elasticity measures (PWV and AI) were similarly unaffected (Figure 3). Compliance assessed as class attendance was not correlated with change in FMD, both in the CRM group (Pearson r=-0.08, p=0.79) and in the HE group (Pearson's r=-0.21, p=0.49).

Metabolic Syndrome Risk Factors

Virtually all the metabolic syndrome risk factors showed beneficial trends in the CRM group, while they showed less benefit or worsening in the HE group (Table 2). In the CRM arm, changes between baseline and 12 months were significant for diastolic BP (-6.2 mm Hg, 95% CI, -11.7 to -0.8 mm Hg, p=0.026), and weight (-2.5 kg, 95% CI, -0.2 to -4.8 kg, p=0.033); additionally, the interaction between treatment arm and time was significant for triglyceride levels, after adjusting for baseline levels (p=0.012) and marginally significant for fasting glucose (p=0.095). The summation score counting the number of metabolic syndrome risk factors tended to decrease in the CRM group and to worsen in the HE group (p=0.049 for the interaction between treatment group and time, Table 2).

Psychosocial and Behavioral Factors

Both interventions significantly improved depressive symptoms and STAI-State anxiety scores. STAI-Trait anxiety and Perceived Stress Scale scores were reduced slightly more in the HE group. No significant changes were observed in anger and hostility measures for both interventions (Table 3). Neither CRM nor HE was associated with significant changes in moderate physical activity. Vigorous physical activity, however, which was log transformed because of its skewed distribution, increased in the CRM group, from a geometric mean of 3.8 ± 4.2 min/day to 9.1 ±3.9 min/day (p=0.023), while it tended to decrease in the HE group (from 10.5± 5.7 min/day to 6.3± 4.3 min/day, p=0.43), p=0.032 for the interaction between group and time. The increase in physical activity, however, did not substantially explain the effect of CRM on FMD. The mean change in FMD in the CRM group decreased only slightly, from 2.1% (95% CI, 0.5 to 3.7%, p=0.009), to 1.9% (95% CI, 0.3 to 3.6%, p=0.022) once vigorous physical activity was added to the model. Changes in BMI also did not contribute to the findings, as there was no significant correlation between changes in BMI and changes in FMD (Pearson's r=0.04, p=0.63).

Metabolic/Inflammatory Biomarkers

Biomarker data were available for 27 participants randomized to HE (82%) and 29 participants randomized to CRM (83%). Adiponectin was slightly higher in the HE than in the CRM group at baseline; there were no differences in the baseline levels of leptin or any of the inflammatory biomarkers (CRP, IL-6, TNF-α and PAI-1) between the two groups. Biomarker data did not change significantly in either group during the follow-up (Table 4).

Discussion

Among black Americans with components of the metabolic syndrome, CRM, a sound-based meditation intervention, did not improve endothelial function significantly more than a

control intervention of health education, which was matched to the CRM intervention for frequency of meetings and time with the instructor. In the CRM group, several metabolic risk factors tended to improve at 12 months, while they did not improve or tended to worsen in the HE group, as did a cumulative metabolic risk score that included BP, weight, glucose, HDL-cholesterol and triglyceride levels. These effects occurred despite no substantial difference in the impact of the interventions on perceived stress and other psychosocial risk factors.

An innovative aspect of our study is the inclusion of an urban black population, a group that remains understudied. While studies have linked chronic psychosocial and environmental stressors, such as social and economic disadvantage and discrimination, to CVD and its risk factors,(38-41) these associations tend to be more pronounced among blacks.(42,43) These differences may in part be mediated by race differences in autonomic nervous system responses and behavioral and psychosocial factors such as depression and anger expression.(39,44,45) For example, community-dwelling blacks have higher rates of discrimination ratings and depressive symptoms than whites,(42,46-48) and these factors tend to be more predictive of hypertension and CVD in blacks than in whites.(42,48-50)

Our results are in agreement with previous clinical trials of stress reduction interventions using meditation that have shown beneficial effects on CVD risk factors.(13,51) Recently, the effects of TM on insulin resistance were examined in 103 patients with clinically-confirmed CVD who were randomized to either TM or a HE control group for 16 weeks; 84 completed the protocol.(52) Consistent with our trial, this study found a significant improvement in BP and other metabolic risk factors in the patients randomized to TM compared to HE. FMD was examined as secondary outcome. There was a non-significant improvement in FMD (0.11%) in the TM group and a non-significant decline in the HE group (-0.81) ($p=0.24$ for difference between groups). Our results are in agreement with this previous report in terms of failing to find a significant between-group difference in FMD, although we did find a somewhat larger (2.1%) improvement in FMD within the meditation group. It should be noted that this earlier trial studied a different population, i.e., patients with established coronary artery disease, many of whom may not have had metabolic syndrome and most of whom had already advanced vascular disease with a limited potential for improvement in endothelial function. In contrast, we excluded persons with previous coronary artery disease and selected participants with metabolic syndrome risk factors.

Several, if not all, of the metabolic syndrome risk factors,(53-55) as well as visceral fat and insulin resistance,(56,57) have been linked to adrenocortical and autonomic disturbances. Recently, in the Chicago site of the Study of Women's Health Across the Nation, both depressive symptoms and experiences of discrimination were associated with visceral fat, an important substrate for metabolic syndrome, but not with subcutaneous fat, both assessed by computed tomography; these relationships were observed both in black and white women.(47,58) Possible effects of stress-reduction on lifestyle behaviors may also play a role. In fact, we found that participants randomized to CRM increased their level of vigorous physical activity more than participants randomized to HE. One might speculate that this reflects an increase in energy level in the CRM group relative to the control group, or an increased focus on personal physical activity goals. Nonetheless, our physical activity assessment was somewhat imprecise and the increase in physical activity did not substantially explain the effects of CRM on FMD.

Limitations of our trial include its small size that limited the power to detect a significant difference in the change in outcome measures between the two randomized groups. The study power was also affected by a smaller than anticipated effect on FMD, and a higher attrition rate. The relatively high drop-out rate, however, is not surprising for a year-long

intervention in an at-risk population, and there was no difference in retention rate between the two randomized groups. Furthermore, we used a statistical approach for unbalanced data that allowed all available data to be included in the analysis. Nonetheless, we recognize that generalizability may be affected. Although participants were masked to the research hypothesis, we were not able to evaluate whether this masking was successful because data on participants' expectations were not collected. It is also possible that baseline differences in metabolic and vascular factors may have influenced the results. However, with exception for triglycerides, the two groups were balanced for baseline factors, and we adjusted for baseline triglyceride levels in the model. Finally, we studied a novel meditation approach, CRM, that has not been evaluated before in a controlled fashion. However, CRM follows closely the TM standardized protocol with few but significant modifications, and has the possible advantage of being more acceptable to community-dwelling blacks. TM has failed to disseminate in the black community, possibly because it requires substantial investment in cost and time. CRM could be more successfully disseminated at the community level. Another advantage of our study is the use of a control intervention that rigorously controlled for frequency and duration of the training sessions, as well as practice time at home. Indeed, a limitation of many previous trials is lack of an adequate control intervention.(11)

In conclusion, among black Americans with metabolic syndrome risk factors, CRM, a sound-based meditation intervention, did not improve endothelial function significantly more than a control intervention of health education. Favorable trends in metabolic risk factors were observed at the end of the 1-year intervention period denoting improvement in the CRM group and no change or worsening in the HE group.

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Abbreviations

BP	Blood Pressure
CRM	Consciously Resting Meditation
CRP	C Reactive Protein
CVD	Cardiovascular Disease
FMD	Flow-Mediated Dilation

HE	Health Education
PWV	Pulse-Wave Velocity
NMD	Nitroglycerin-Mediated Vasodilation
TM	Transcendental Meditation

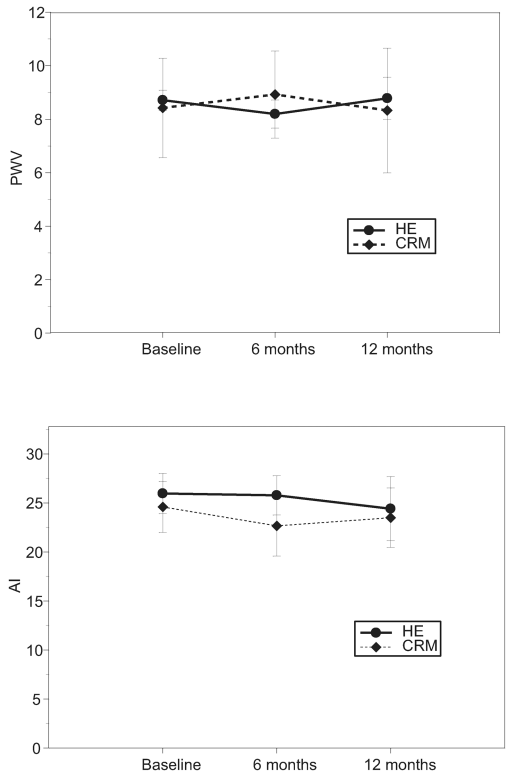

Figure 1.
CONSORT flow diagram for enrollment and follow-up of study participants.

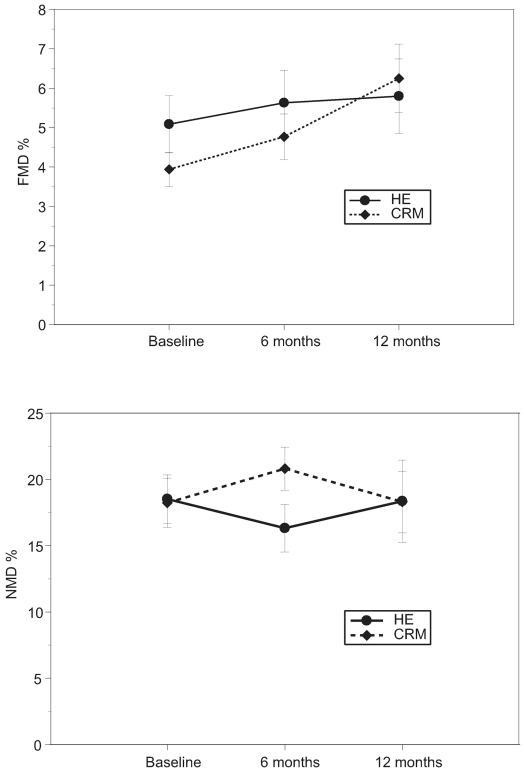

Figure 2.
Brachial artery reactivity testing results by intervention group, including flow-mediated vasodilation (FMD %) and endothelium-independent nitroglycerin-mediated vasodilation (NMD%).

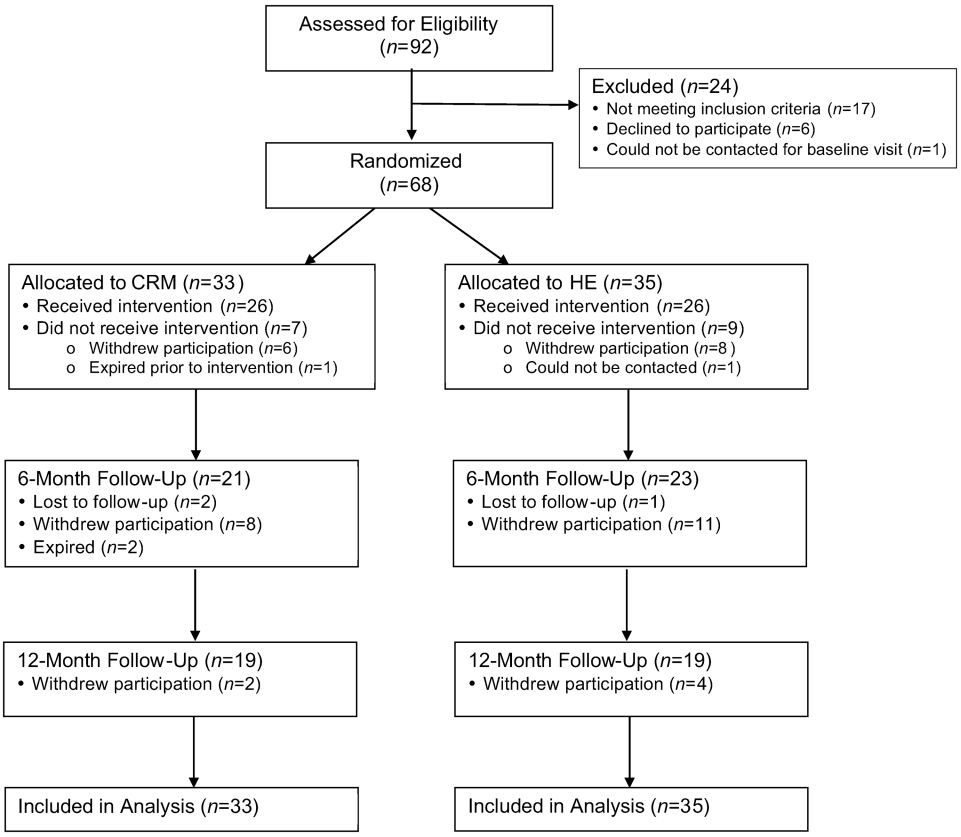

Figure 3.
Arterial stiffness results by intervention group, including pulse wave velocity (PWV) and augmentation index (AI).

Table 1

Baseline demographics and risk factors by intervention group.

Measure	CRM (n=33)	HE (n=35)
Demographic Factors		
Age (years), mean (SD)	51.5 (7.5)	52.1 (7.6)
Male, %	25.0	17.1
Married, %	37.5	34.3
More than high school education, %	76.7	78.1
Metabolic Risk Factors and Medical History		
Body mass index (kg/m^2), mean (SD)	38.2 (11.2)	36.7 (5.6)
Systolic blood pressure (mm Hg), mean (SD)	138.5 (22.2)	137.5 (21.4)
Diastolic blood pressure (mm Hg), mean (SD)	83.2 (13.1)	83.5 (12.2)
Heart rate (beat/min), mean (SD)	73.7 (11.8)	70.9 (13.7)
LDL-cholesterol (mg/dL), mean (SD)	117.3 (32.8)	121.0 (44.0)
HDL-cholesterol (mg/dL), mean (SD)	54.1 (15.3)	55.0 (11.1)
Triglycerides (mg/dL), mean (SD)	137.9 (80.8)	102.7 (50.2)
Creatinine (mg/dL), mean (SD)	0.96 (0.31)	0.84 (0.25)
Glucose (mg/dL) mean (SD)	116.8 (57.4)	100.3 (38.3)
Insulin (μIU/mL), mean (SD)	18.3 (31.1)	14.1 (12.9)
History of diabetes, %	45.5	41.2
HOMA index	1.04	0.92
Family history of heart disease before age 55, %	37.9	39.4
Moderate physical activity, minutes/day (SD)	167 (228)	230 (242)
Vigorous physical activity, minutes/day (SD)	10.5 (23.8)	38.3 (75.9)
Medications		
On aspirin, %	21.2	14.3
On statins, %	45.5	25.7
On beta blockers, %	18.2	20.0
On ACE Inhibitors, %	27.3	28.6
Psychosocial Risk Factors		
Spielberger's Anger-in, mean (SD)	14.4 (3.9)	14.0 (4.0)
Spielberger's Anger-out, mean (SD)	12.9 (3.4)	13.0 (2.5)
Cook-Medley Hostility Inventory, mean (SD)	17.2 (8.1)	18.0 (7.4)
Cohen's Perceived Stress Scale, mean (SD)	14.8 (8.4)	17.4 (8.6)
Spielberger's State Anxiety, mean (SD)	36.8 (13.2)	40.0 (14.1)
Spielberger's Trait Anxiety, mean (SD)	38.2 (11.9)	39.5 (12.4)
Beck Depression Inventory II, mean (SD)	10.9 (7.7)	11.0 (9.7)
Beck Depression Somatic Subscore, mean (SD)	0.64 (0.44)	0.59 (0.48)
Beck Depression Cognitive Subscore, mean (SD)	2.6 (3.1)	3.3 (3.9)

* Based on log-transformed values.

Table 2

Changes in flow-mediated vasodilation (FMD) and metabolic risk factors by study group.

		Study Visit Means ± SD					
Variable	**Study Group**	**Baseline**	**6 Months**	**12 Months**	**Change, Baseline to 12 Months (95% CI)***	***P* Value for Trend Within Group**	***P* Value for group difference in trend**
FMD %	CRM	3.9 (2.4)	4.8 (2.7)	6.3 (3.3)	2.10 (0.53, 3.67)	0.009	0.51
	HE	5.1 (4.2)	5.6 (4.4)	5.8 (3.4)	1.36 (-0.24, 2.95)	0.094	
SBP, mm Hg	CRM	138.2 (22.3)	135.9 (20.5)	129.6 (11.1)	-3.84 (-13.07, 5.38)	0.41	0.78
	HE	137.5 (21.5)	132.7 (25.2)	133.4 (20.1)	-2.08 (-11.02, 6.86)	0.64	
DBP, mm Hg	CRM	83.1 (13.0)	83.1 (15.8)	74.1 (11.1)	-6.24 (-11.71, -0.77)	0.026	0.17
	HE	83.5 (12.2)	79.6 (14.0)	82.3 (15.3)	-0.97 (-6.27, 4.33)	0.72	
Weight, Kg	CRM	104.8 (32.7)	101.8 (30.9)	100.6 (23.2)	-2.52 (-0.20, -4.83)	0.033	0.26
	HE	101.1 (15.1)	102.0 (15.5)	101.0 (16.8)	-0.69 (-1.51, 2.89)	0.54	
BMI	CRM	37.7 (11.2)	36.8 (10.6)	37.5 (9.8)	-0.99 (0.13, 1.86)	0.025	0.34
	HE	36.7 (5.6)	37.0 (5.0)	36.3 (4.9)	-0.43 (-0.38, 1.23)	0.29	
Glucose, mg/dL	CRM	117.5 (58.2)	138.5 (68.8)	111.2 (34.7)	-6.04 (-28.02, 15.94)	0.59	0.095
	HE	100.3 (38.3)	112.4 (52.6)	128.1 (58.9)	20.86 (-1.90, 43.63)	0.072	
Insulin, mU/L	CRM	18.2 (31.6)	18.4 (21.3)	14.2 (9.6)	-1.13 (-9.12, 6.85)	0.78	0.68
	HE	14.1 (12.9)	16.4 (14.8)	16.9 (24.7)	1.22 (-6.90, 9.34)	0.77	
Triglycerides, mg/dL	CRM	136.9 (81.9)	128.9 (57.8)	109.6 (36.6)	-14.35 (-31.75, 3.06)	0.10	0.012
	HE	102.7 (50.2)	109.4 (58.1)	123.8 (90.1)	17.72 (-0.19, 35.63)	0.052	
HDL-C, mg/dL	CRM	54.2 (15.5)	55.7 (17.1)	57.1 (17.5)	1.47 (-2.04, 4.97)	0.41	0.71
	HE	55.0 (11.1)	54.8 (9.7)	56.3 (12.2)	0.51 (-3.14, 4.16)	0.70	
Metabolic syndrome score	CRM	2.8 (1.1)	2.8 (1.1)	2.3 (1.2)	-0.41 (-0.89, 0.06)	0.089	0.049
	HE	2.5 (0.8)	2.3 (1.0)	2.7 (1.2)	0.25 (-0.21, 0.72)	0.28	

*Model estimates, adjusted for individual variance, obtained using repeated measures mixed effects models. Mean estimates for triglyceride are adjusted for baseline triglyceride values.

FMD: flow-mediated vasodilation; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 3

Changes in psychosocial scale scores by study group.

		Study Visit Means ± SD					
Variable	**Study Group**	**Baseline**	**6 Months**	**12 Months**	**Change, Baseline to 12 Months (95% CI)***	***P* Value for Trend Within Group**	***P* Value for group difference in trend**
Anger-in	CRM	14.4 (3.9)	14.1 (3.8)	13.7 (3.4)	-0.35 (-1.69, 0.99)	0.60	0.71
	HE	14.0 (4.0)	13.4 (3.5)	13.3 (3.6)	0.0002 (-1.33, 1.33)	1.00	
Anger-out	CRM	12.9 (3.4)	12.2 (3.2)	13.4 (3.7)	0.34 (-0.76, 1.45)	0.54	0.52
	HE	13.0 (2.5)	13.5 (3.2)	12.4 (2.5)	-0.17 (-1.27, 0.93)	0.76	
Hostility	CRM	17.2 (8.1)	17.6 (8.0)	17.7 (8.0)	1.69 (-0.46, 3.84)	0.12	0.10
	HE	18.0 (7.4)	16.7 (8.4)	15.4 (6.7)	-0.84 (-2.98, 1.30)	0.44	
PSS	CRM	14.8 (8.4)	14.0 (6.9)	12.1 (6.2)	-1.66 (-4.42, 1.11)	0.24	0.022
	HE	17.4 (8.6)	14.0 (7.7)	9.4 (6.4)	-6.50 (-9.55, -3.45)	<0.001	
STAI-State	CRM	36.8 (13.2)	32.4 (10.1)	28.4 (7.7)	-6.63 (-10.73, -2.53)	0.002	0.65
	HE	40.0 (14.1)	35.8 (11.0)	31.7 (7.6)	-8.01 (-12.40, -3.62)	0.001	
STAI-Trait	CRM	38.2 (11.9)	34.4 (11.1)	33.4 (8.7)	-2.43 (-5.22, 0.37)	0.088	0.48
	HE	39.5 (12.4)	37.7 (13.5)	33.2 (8.6)	-3.88 (-6.87, -0.88)	0.012	
BDI-Somatic	CRM	0.6 (0.4)	0.5 (0.3)	0.3 (0.2)	-0.19 (-0.34, -0.05)	0.011	0.72
	HE	0.6 (0.5)	0.5 (0.4)	0.4 (0.4)	-0.16 (-0.31, -0.01)	0.040	
BDI-Cognitive	CRM	2.6 (3.1)	1.7 (2.1)	0.6 (0.8)	-1.34 (-2.48, -0.21)	0.021	0.87
	HE	3.3 (3.9)	2.6 (3.5)	1.2 (1.6)	-1.47 (-2.61, -0.34)	0.011	
BDI-Total	CRM	10.9 (7.7)	7.8 (5.4)	5.1 (3.3)	-3.76 (-6.38, -1.15)	0.005	0.86
	HE	11.0 (9.7)	9.0 (7.8)	6.1 (6.0)	-3.44 (-6.04, -0.84)	0.010	

*Model estimates, adjusted for individual variance, obtained using repeated measures mixed effects models.

PSS: Perceived Stress Scale; STAI: State-Trait Anxiety Inventory; BDI: Beck Depression Inventory.

Table 4

Changes in biomarker levels by study group.

		Study Visit Means ± SD					
Variable	**Study Group**	**Baseline**	**6 Months**	**12 Months**	**Change, Baseline to 12 Months (95% CI)***	***P* Value for Trend Within Group**	***P* Value for group difference in trend**
Leptin (ng/mL)	CRM	71.1 (40.6)	77.2 (40.4)	72.5 (46.9)	-3.77 (-16.54, 9.00)	0.56	0.65
	HE	70.4 (37.4)	71.5 (39.9)	67.5 (37.2)	0.36 (-12.53, 13.24)	0.96	
LgAdiponectin (ng/mL)	CRM	9.0 (0.5)	9.0 (0.5)	9.0 (0.4)	0.05 (-0.13, 0.23)	0.58	0.40
	HE	9.2 (0.4)	9.0 (0.4)	9.2 (0.5)	-0.06 (-0.24, 0.12)	0.52	
LgCRP (mg/L)	CRM	1.2 (1.2)	1.2 (0.8)	1.1 (1.1)	-0.04 (-0.41, 0.32)	0.81	0.24
	HE	1.4 (1.1)	1.4 (1.0)	1.6 (1.0)	0.27 (-0.11, 0.64)	0.16	
LgIL-6 (pg/mL)	CRM	0.1 (1.0)	0.3 (1.0)	0.3 (0.6)	0.16 (-0.29, 0.62)	0.47	0.57
	HE	0.1 (1.2)	0.3 (1.5)	0.6 (1.0)	0.35 (-0.10, 0.79)	0.13	
TNF-α (pg/mL)	CRM	2.3 (1.3)	2.8 (1.2)	2.4 (1.6)	-0.13 (-0.69, 0.44)	0.66	0.24
	HE	2.4 (1.8)	3.4 (1.5)	3.4 (1.4)	0.35 (-0.22, 0.92)	0.23	
LgPAI-1 (pg/mL)	CRM	10.3 (1.0)	10.2 (0.5)	10.0 (0.7)	-0.03 (-0.41, 0.36)	0.89	0.95
	HE	10.4 (1.1)	9.9 (0.8)	9.9 (0.7)	-0.01 (-0.40, 0.38)	0.96	

*Model estimates, adjusted for individual variance, obtained using repeated measures mixed effects models.

CRP: C-reactive protein; IL-6: interleukin 6; TNF-α: tumor necrosis factor α. PAI-1: plasminogen activator inhibitor 1.