Effects of a Randomized Controlled Trial of Transcendental Meditation on Components of the Metabolic Syndrome in Subjects With Coronary Heart Disease

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Background: The metabolic syndrome is thought to be a contributor to coronary heart disease (CHD), and components of the syndrome have been identified as possible therapeutic targets. Previous data implicate neurohumoral activation related to psychosocial stress as a contributor to the metabolic syndrome. The aim of this study was to evaluate the efficacy of transcendental meditation (TM) on components of the metabolic syndrome and CHD.

Methods: We conducted a randomized, placebo-controlled clinical trial of 16 weeks of TM or active control treatment (health education), matched for frequency and time, at an academic medical center in a total of 103 subjects with stable CHD. Main outcome measures included blood pressure, lipoprotein profile, and insulin resistance determined by homeostasis model assessment (calculated as follows: [(fasting plasma glucose level [in milligrams per deciliter] × fasting plasma insulin level [in microunits per milliliter]) × 0.0552]/22.5); endothelial function measured by brachial artery reactivity testing; and cardiac autonomic system activity measured by heart rate variability.

Results: The TM group had beneficial changes (measured as mean ± SD) in adjusted systolic blood pressure (–3.4 ± 2.0 vs 2.8 ± 2.1 mm Hg; $P = .04$), insulin resistance (–0.75 ± 2.04 vs 0.52 ± 2.84; $P = .01$), and heart rate variability (0.10 ± 0.17 vs –0.50 ± 0.17 high-frequency power; $P = .07$) compared with the health education group, respectively. There was no effect of brachial artery reactivity testing.

Conclusions: Use of TM for 16 weeks in CHD patients improved blood pressure and insulin resistance components of the metabolic syndrome as well as cardiac autonomic nervous system tone compared with a control group receiving health education. These results suggest that TM may modulate the physiological response to stress and improve CHD risk factors, which may be a novel therapeutic target for the treatment of CHD.

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THE METABOLIC SYNDROME, characterized by the clustering of hypertension, dyslipidemia, visceral obesity, and insulin resistance, is now regarded as a risk factor for cardiovascular morbidity and mortality[1] and is recognized as a new means of detecting coronary heart disease (CHD) risk.[2] The metabolic syndrome prevalence is rising rapidly concomitant with the obesity epidemic, fueled by physical inactivity and unhealthy eating patterns.[3] Rates of metabolic syndrome–associated CHD are projected to increase substantially.[3,4]

Insulin resistance is regarded by many researchers as a key component of the metabolic syndrome, with interesting parallels to the insulin-resistant type of diabetes. Both are related to visceral obesity[5] and both are associated with hypertension; however, lean hypertensive patients can be insulin resistant.[5,6] Additional findings have drawn a link to the sympathoadrenal system, suggesting that neurohumoral activation may be causally involved.[5-7] Visceral obesity, insulin resistance, and diabetes are also associated with a proinflammatory state,[8] which is associated with increased CHD risk.[9] However, whether there is an underlying causal mechanism of the metabolic syndrome such as neurohumoral activation or whether it simply represents a cluster of risk factors that are not causally related is unknown.

Randomized controlled trials of transcendental meditation (TM) have demonstrated a blood pressure–lowering effect similar to a first-line antihypertensive medication compared with a control intervention of health education (HE).[10-14] These results suggest that TM may have a beneficial impact on certain underlying

risk factors for CHD, including blood pressure, via neurohumoral alterations in the sympathetic nervous system activity. Whether such effects occur on other CHD risk factors, including those encompassed within the metabolic syndrome, has not been previously studied. Therefore, we undertook a randomized, controlled trial of 16 weeks of TM compared with HE in 103 patients with stable CHD on the main components of the metabolic syndrome and CHD, including blood pressure, lipoprotein profile, and insulin resistance determined by homeostasis model assessment (HOMA) (calculated as follows: [(fasting plasma glucose level [in milligrams per deciliter] × fasting plasma insulin level [in microunits per milliliter]) × 0.0552]/22.5, as well as endothelial function measured by brachial artery reactivity testing (BART) and cardiac autonomic nervous system activity measured by heart rate variability (HRV).

METHODS

STUDY DESIGN AND POPULATION

The study design was a randomized, single-blind, attention-controlled trial. Patients were recruited from a supervised cardiac exercise and rehabilitation program at Cedars-Sinai Medical Center and the surrounding community. We included women and men older than 18 years, with CHD documented by prior myocardial infarction, coronary artery bypass surgery, coronary angiography, or angioplasty. Exclusion criteria consisted of unstable coronary syndromes, congestive heart failure greater than New York Heart Association class III, renal failure, acute myocardial infarction in the preceding 3 months, atrial fibrillation or a predominantly paced rhythm, prior TM, or current stress management practice. The study was approved by the institutional review board, and all participants gave written informed consent.

STUDY PROTOCOL

Randomization to TM or to HE for 16 weeks was performed via a computerized program with blocking, whereby eligible patients were grouped according to age (≥65 years) and low-density lipoprotein cholesterol levels (≥120 mg/dL [≥6.66 mmol/L]) and assigned to treatment group accordingly. Once a group of 10 to 16 patients was randomized (ie, 5-8 per treatment group), a new cohort would be formed and begin the respective interventions concomitantly. The outcome data were collected and analyzed by personnel blinded to patient treatment status. At study entry and exit, after an overnight fast, patients underwent a medical history review, including cardiac risk factors, physical activity level, psychosocial variables, and medication assessment, along with BART, 24-hour ambulatory Holter monitoring of HRV, and blood sampling. Compliance with the TM and HE programs was assessed by class attendance and self-reported compliance. The blood pressure protocol included 5 minutes of sitting quietly followed by blood pressure measurement using a mercury sphygmomanometer 3 times at 1-minute intervals, and then averaged for screening and entry and exit visits.[15] Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Psychosocial assessment included indicators of hostility,[16] typical depression,[17] trait anxiety and anger,[18] and life stress.[19]

TM AND HE INTERVENTIONS

The TM technique is a meditation modality restored from the ancient Vedic tradition in India[16] and taught worldwide since 1957.[20] The highly standardized and reproducible TM teaching materials were used to ensure quality control and consistency. The format of TM includes 2 introductory lectures (1.5 hours each), personal interview (usually 10-15 minutes), personal instruction (1-1.5 hours), 3 group meetings (1.5 hours each), and follow-up and maintenance meetings (1.5 hours) twice per week for the first 4 weeks and weekly thereafter. Subjects randomized to HE attended the same number, size, and frequency of group meetings led by professional health educators as the TM group. The lectures and discussions included CHD risk factors and the impact of stress, diet, and exercise on CHD. Daily home assignments were given to control for home TM practice time.

BLOOD TESTING AND HOMA PROTOCOL

Levels of total plasma cholesterol, triglycerides, and high-density lipoprotein cholesterol were determined as previously published.[21] Plasma glucose and plasma insulin concentrations were measured using a commercially available glucose reagent (Elan Corporation, Dublin, Ireland)[22] and automated immunoassay instrument and ultrasensitive insulin kit (Beckman-Coulter, Fullerton, Calif),[23] respectively. Assays were performed in batches and in duplicate. The degree of insulin resistance in each subject was estimated by means of the HOMA using the following formula: ([fasting plasma glucose level (in milligrams per deciliter) times fasting plasma insulin level (in microunits per milliliter)] × 0.0552)/22.5, according to the method[21] where high values indicate high insulin resistance. Prior study has documented the reliability of HOMA by comparison with the euglycemic-hyperinsulinemic clamp technique.[24,25]

BART PROTOCOL

Patients fasted overnight and were withdrawn from vasoactive medication therapy 24 to 48 hours before testing, as per our standard protocol.[26] We assessed (1) peripheral flow-mediated, endothelium-dependent vasomotion and (2) endothelium-independent vasodilation in the brachial artery using a noninvasive high-resolution B-mode ultrasonography technique, as previously described,[27] using our validated analytical methods to measure flow-mediated dilation.[28]

HRV PROTOCOL

Results of Holter monitoring were collected during a 24-hour period using our previously validated and published methods.[29] A 24-hour tape was considered eligible for this study if it had more than 12 hours of analyzable data and half of the nighttime and daytime periods analyzable, and if more than 50% of the recording demonstrates sinus rhythm. The HRV was analyzed using commercially available software (Marquette software, version 002A; Marquette University, Milwaukee, Wis).

STATISTICAL ANALYSIS

Data are presented as mean±SD for continuous variables and as frequencies and percentages for categorical variables. Comparison of treatment groups at entry and exit was performed using paired and unpaired *t* test for continuous data and χ^2 and Fisher exact tests for discrete data. The Wilcoxon signed rank and rank sum tests were used for the analysis of nonnormally distributed continuous variables. Multivariable regression was performed using general linear methods to determine least square

Table 1. Entry Clinical Characteristics by Intervention Group*

Characteristic	TM Group (n = 52)	HE Group (n = 51)	*P* Value†
Age, mean ± SD, y	67.7 ± 9.0	67.1 ± 10.5	.78
Male	41 (79)	43 (84)	.47
BMI, mean ± SD	28.3 ± 4.5	28.3 ± 4.6	.90
History of hypertension	32 (62)	27 (53)	.44
History of diabetes	9 (17)	9 (18)	.99
Previous MI	30 (58)	20 (39)	.07
Previous revascularization	47 (90)	48 (94)	.97
Current smoking	0	1 (2)	.97
Statin use	43 (83)	43 (84)	.99
ACE/AII inhibitor use	22 (42)	23 (45)	.99
Calcium channel blocker use	10 (19)	16 (31)	.17
β-Blocker use	24 (46)	20 (39)	.42
Moderate and vigorous exercise activity, mean ± SD, h/d	4.6 ± 3.7	4.5 ± 3.3	.92

Abbreviations: AII, angiotensin II; ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HE, health education; TM, transcendental meditation.

*Unless otherwise indicated, data are expressed as number (percentage) of patients.

†Calculated by the Wilcoxon *t* test for determining differences between the 2 treatment groups.

means of the dependent variable of interest, adjusting for independent variables as appropriate. To control for the effect that entry measurements may exert on exit measurements, models were adjusted for entry values. Bonferroni adjustment for multiple outcomes was used to adjust the significance level for the 3 spectral domain HRV outcomes hypothesized to be affected by the intervention. A *P* value less than .05 was required for statistical significance. Analyses were performed using SAS software, version 8.1 (SAS Institute Inc, Cary, NC).

RESULTS

Overall, 103 patients enrolled and 84 (82%) completed the study. Among the 19 dropouts, 12 were in the HE group and 15 dropped out before starting either intervention owing to lack of interest in group assignment. Compliance, assessed by class attendance, was 97% (7 dropouts) in the TM and 88% (12 dropouts) in the HE groups (*P*=.19). No adverse events were reported.

Entry clinical characteristics for the TM and HE groups are given in **Table 1** and demonstrate a predominantly male, older CHD population with high rates of treated hypertension, dyslipidemia, and obesity. Few of the patients had diabetes. Medical management of CHD was near-optimal, with high rates of lipid-lowering, angiotensin-converting enzyme inhibitor, and β-blocker medication use. Most patients performed regular physical activity in a cardiac rehabilitation program.

STUDY OUTCOMES

Blood Pressure, Lipoprotein Levels, and Other Cardiac Risk Factors

We observed significant group differences in exit systolic blood pressure and mean arterial blood pressure in the TM compared with the HE group (**Table 2**). Unadjusted change (Δ) in systolic blood pressure was –3.3±12.2 vs 1.7±15.4 mm Hg in the TM vs HE group (*P*=.12). Adjustment for age, sex, baseline systolic blood pressure, history of myocardial infarction, baseline depression and anger, exit

Table 2. Blood Pressure, Lipoprotein Levels, and Other Risk Factors by Intervention Group*

Variable	TM Group	HE Group	*P* Value†
Systolic blood pressure, mm Hg			
Entry	126.4 ± 14.4	127.4 ± 15.5	.99
Exit	123.5 ± 14.9	130.5 ± 16.1	.03
Diastolic blood pressure, mm Hg			
Entry	73.8 ± 9.7	76.2 ± 9.2	.23
Exit	73.4 ± 8.4	76.5 ± 9.9	.14
Mean arterial blood pressure, mm Hg			
Entry	90.3 ± 9.1	91.7 ± 9.5	.38
Exit	90.1 ± 9.0	94.5 ± 10.9	.03
Total cholesterol level, mg/dL			
Entry	166.4 ± 31.4	176.4 ± 33.2	.11
Exit	158.6 ± 24.2	167.9 ± 28.6	.22
Triglyceride level, mg/dL			
Entry	135.1 ± 77.4	151.6 ± 84.6	.26
Exit	126.7 ± 56.2	152.8 ± 84.9	.28
HDL-C level, mg/dL			
Entry	47.0 ± 13.1	49.4 ± 14.1	.34
Exit	44.3 ± 8.3	48.3 ± 14.7	.57
LDL-C level, mg/dL			
Entry	92.6 ± 25.2	96.5 ± 27.8	.44
Exit	89.0 ± 21.5	92.8 ± 30.8	.99
High-sensitivity CRP level, mg/dL			
Entry	2.1 ± 2.4	3.2 ± 5.4	.79
Exit	2.9 ± 4.8	2.3 ± 2.7	.98
Exercise score, h/wk‡			
Entry	4.6 ± 3.7	4.5 ± 3.3	.92
Exit	4.3 ± 3.5	5.6 ± 3.5	.09
Anger score§			
Entry	17.9 ± 8.5	21.5 ± 9.7	.052
Exit	15.3 ± 7.1	18.9 ± 8.7	.04
Depression score‖			
Entry	6.8 ± 7.1	12.2 ± 10.7	.003
Exit	7.1 ± 6.9	11.2 ± 10.0	.053
Anxiety score¶			
Entry	14.4 ± 10.1	17.8 ± 11.7	.17
Exit	12.8 ± 7.9	15.8 ± 11.4	.31
Life stress score#			
Entry	1.7 ± 1.8	2.3 ± 2.5	.22
Exit	1.4 ± 1.4	1.9 ± 1.7	.24

Abbreviations: CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HE, health education; LDL-C, low-density lipoprotein cholesterol; TM, transcendental meditation.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259; triglyceride to millimoles per liter, multiply by 0.0113.

*Data are expressed as mean ± SD. For the HE group, n = 51 at entry and n = 39 at exit; for the TM group, n = 52 at entry and n = 45 at exit.

†Determined by Wilcoxon nonparametric test.

‡Determined by the Physical Activity Questionnaire according to hours per week of moderate to vigorous exercise.

§Determined by anger questionnaire.

‖Determined by the Center for Epidemiolgical Studies Depression Scale.

¶Determined by the Speilberger Trait Anxiety Inventory questionnaire.

#Determined by the Life Stress Instrument questionnaire.

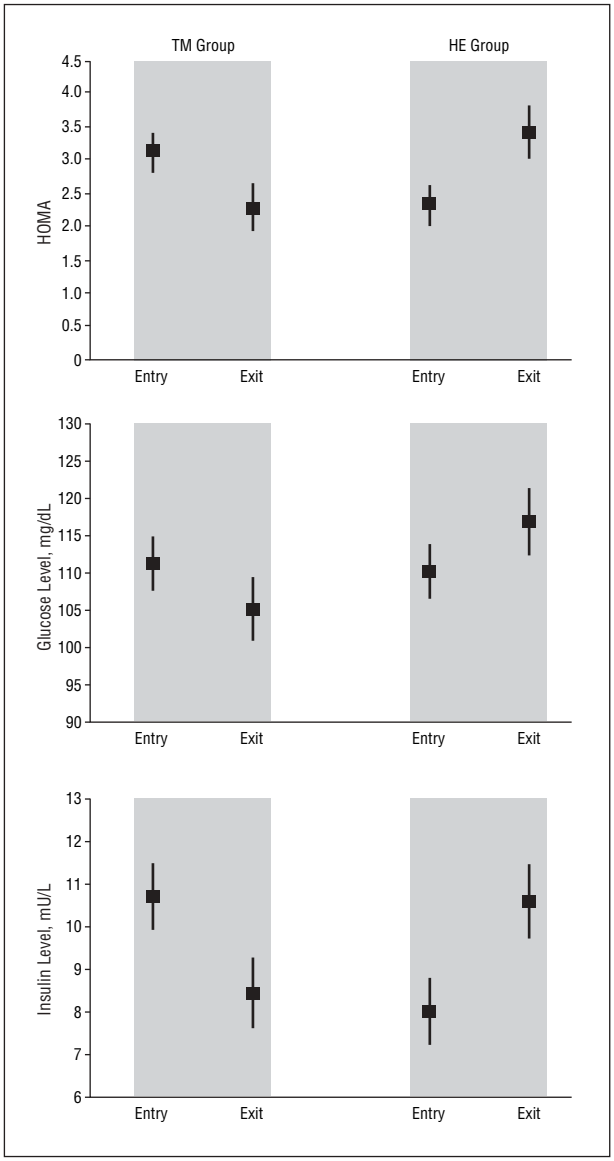

Figure. Homeostasis model assessment (HOMA) as a measure of insulin resistance and blood glucose and insulin levels by intervention group. We calculated HOMA according to the following formula: ([fasting plasma glucose level (in milligrams per deciliter) × fasting plasma insulin level (in microunits per milliliter)] × 0.0552)/22.5. High HOMA values indicate high insulin resistance. Entry values were adjusted for age, sex, and history of diabetes. Exit values and change variables are also adjusted for baseline value. For differences between the transcendental meditation (TM) vs health education (HE) groups at exit, $P = .03$ for insulin resistance; $P = .06$ for glucose level; and $P = .02$ for insulin level. For within-group change, $P = .06$ for insulin resistance in the TM group; $= P = .04$ for glucose level in the TM group. For the TM group, n = 52 at entry and n = 45 at exit; for the HE group, n = 51 at entry and n = 39 at exit. To convert glucose to millimoles per liter, multiply by 0.0555; insulin to picomoles per liter, multiply by 6.945.

BMI, and physical activity level increased the difference in systolic blood pressure changes (–3.4 ± 2.0 vs 2.8 ± 2.1 mm Hg, TM vs HE groups [$P = .04$]). There were no differences from entry to exit levels of lipoproteins and high-sensitivity C-reactive protein or BMI in either treatment group, but a marginally significant increase in physical activity level was observed in the HE group ($P = .09$). The HE group was significantly more depressed and angry compared with the TM group at trial entry, and this did not change at exit. There was no difference in self-reported life stress, which was low overall in both groups. Adjustment for entry variables, medication, or intervention completion did not alter any of these results.

Table 3. BART Finding by Intervention Group*

BART Finding	TM Group	HE Group	*P* Value
Entry	n = 51	n = 51	
Resting baseline diameter, mm	4.76 ± 0.91	4.63 ± 0.87	.46
Peak hyperemia diameter, mm	5.01 ± 0.92	4.92 ± 0.85	.61
% FMD	5.67 ± 3.87	6.79 ± 4.50	.18
Exit	n = 45	n = 39	
Resting baseline diameter, mm	4.75 ± 0.92	4.72 ± 0.88	.87
Peak hyperemia diameter, mm	5.01 ± 0.90	5.02 ± 0.87	.99
% FMD	5.92 ± 3.97	6.61 ± 3.24	.38
ΔExit – entry	n = 45	n = 39	
Δ% FMD, unadjusted	–0.08 ± 3.76	0.30 ± 4.25	.67
Δ% FMD†	–0.11 ± 0.50	0.81 ± 0.55	.24

Abbreviations: BART, brachial artery reactivity testing; Δ, change; FMD, flow-mediated dilation (defined as [(diameter after cuff deflation minus diameter at baseline) divided by diameter at baseline] × 100); HE, health education; TM, transcendental meditation.

*Unless otherwise indicated, data are expressed as mean ± SD.

†Adjusted for age, sex, baseline FMD, change in systolic blood pressure from entry to exit, calcium channel blocker use, history of myocardial infarction, and baseline depression and anger scores. Data are expressed as least squares mean ± SE.

Fasting Blood Glucose and Insulin Levels and HOMA

Fasting blood glucose and insulin levels were beneficially improved from entry to exit in the TM compared with the HE group (**Figure**). Unadjusted ΔHOMA from entry to exit within the TM group was –0.79 ± 2.04 ($P = .01$) compared with 0.60 ± 2.84 ($P = .42$) in the HE group, and the ΔHOMA was significantly different between the 2 intervention groups ($P = .03$). This beneficial improvement remained after removing diabetic patients from the analysis (ΔHOMA, –0.49 ± 1.17 in the TM group [$P = .02$] vs –0.07 ± 1.17 in the HE group [$P = .96$]). Similar results for the entire cohort were observed after adjustment for baseline HOMA, diabetes, age, and sex (ΔHOMA, –0.75 ± 2.04 vs 0.52 ± 2.84 [$P = .01$]). Additional adjustment for entry anger and depression and exit physical activity and BMI did not significantly alter the results (–0.80 ± 0.40 in the TM group vs 0.47 ± 0.42 in the HE group [$P = .04$]). Analysis of the diabetic subjects separately (n = 8), demonstrated greater ΔHOMA among the TM vs HE diabetic patients (–2.22 ± 3.94 [$P = .046$] vs 2.59 ± 5.37 [$P = .46$]).

Brachial Artery Reactivity Testing

There were no significant differences in the BART variables from entry to exit, or between groups (**Table 3**). Similar results were found when exit baseline diameters varying by more than 15% from entry baseline diameter were excluded from the analyses (1 patient in the TM group and 3 in the HE group). Adjustment for entry BART variables and medications did not alter the results.

Table 4. HRV by Intervention Group*

HRV Finding	TM Group	HE Group	*P* Value
Entry	n = 47	n = 46	
Total power, log(ms^2)	6.52 ± 1.04	6.69 ± 1.02	.29
High-frequency power, log(ms^2)	4.39 ± 1.12	4.51 ± 1.32	.65
Low-frequency power, log(ms^2)	5.40 ± 1.10	5.58 ± 1.16	.42
Exit	n = 43	n = 35	
Total power, log(ms^2)	6.55 ± 0.79	6.56 ± 0.95	.58
High-frequency power, log(ms^2)	4.44 ± 0.94	4.37 ± 1.22	.86
Low-frequency power, log(ms^2)	5.46 ± 0.88	5.42 ± 1.11	.83
ΔExit – entry†	n = 43	n = 35	
ΔTotal power	–0.01 ± 0.18	–0.49 ± 0.19	.27
ΔHigh-frequency power	0.10 ± 0.17	–0.50 ± 0.17	.07
ΔLow-frequency power	–0.01 ± 0.18	–0.47 ± 0.18	.27

Abbreviations: Δ, change; HE, health education; HRV, heart rate variability; TM, transcendental meditation.

*The spectral domain data contain the total power (0.01-1.00 Hz), low-frequency band (0.04 to <0.15 Hz), and high-frequency band (0.15 to <0.40 Hz) on a 24-hour basis. Unless otherwise indicated, data are expressed as mean ± SD.

†Adjusted for age, sex, baseline HRV variable, body mass index at exit, physical activity level, history of myocardial infarction, and depression and anger scores at baseline. Data are expressed as least squares mean ± SE. The *P* values are Bonferroni adjusted to account for multiple outcome comparisons.

Heart Rate Variability

There were no statistically significant differences between the TM and HE groups with respect to unadjusted entry and exit HRV measures of the spectral or time domain measures. Among the spectral domain measures (**Table 4**), after adjustment for age, sex, baseline HRV measure, history of myocardial infarction, BMI at study exit, physical activity level at study exit, and baseline depression and anger scores, there was a statistically significant difference in Δhigh-frequency power between the TM and HE groups ($P=.02$) (Table 4). After Bonferroni adjustment of the *P* value, the group difference in Δhigh-frequency power became marginally statistically different ($P=.07$). There were also marginally statistically significant differences in adjusted Δtotal power and Δlow-frequency measures (both $P=.09$).

COMMENT

The present study demonstrated that 16 weeks of TM resulted in significant beneficial effects on adjusted blood pressure, insulin resistance, and cardiac autonomic nervous system tone compared with the HE control group. These physiological effects were accomplished without changes in body weight, medication, or psychosocial variables and despite a marginally statistically significant increase in physical activity in the HE group. These results suggest that TM may modulate the physiological response to stress via neurohumoral activation, which may be a novel therapeutic target for the treatment of CHD.

Additional lines of evidence have indirectly suggested that neurohumoral activation may be a common mechanistic pathway for the metabolic syndrome. Previous work by Reaven et al[5] and Brook and Julius[6] has suggested that sympathoadrenal system activation is linked with the metabolic syndrome. Visceral obesity, insulin resistance, and diabetes are also associated with a proinflammatory state[4,8] that is linked with elevated CHD risk.[9] Post hoc analyses of large randomized trials of angiotensin-converting enzyme inhibitors and statins in at-risk subjects have demonstrated reductions in the onset of diabetes.[30-33] Because these classes of medications appear to interrupt important neurohumoral and inflammatory pathways, such results suggest a common causal mechanism for the metabolic syndrome. The present study results expand this understanding and demonstrate that TM, which is believed to reduce sympathoadrenal system activation, beneficially alters the blood pressure and insulin resistance components of the metabolic syndrome. Although a previous meta-analysis demonstrated that educational psychosocial interventions improve glucose control in diabetic patients via improved compliance with medical regimens,[34] the present study results demonstrate an improvement in insulin resistance in nondiabetic patients that was not related to medication change.

These current results also expand our causal understanding of the role of stress in the rising epidemic of the metabolic syndrome. Although current low levels of physical activity, unhealthy eating habits, and resultant obesity are triggers for this epidemic, the demands of modern society may also be responsible for higher levels of chronic stress.[35] Stress activates the neurohumoral system, specifically the sympathoadrenal system and the hypothalamic-pituitary-adrenocortical axis that involves catecholamine release, vagal withdrawal, cortisol secretion, and upregulation of the renin-angiotensin system.[36] Acute psychological stress has also been demonstrated to increase interleukin 6 levels,[37] possibly owing to stress-induced catecholamine activiation. Interleukin 6 also appears to activate the hypothalamic-pituitary-adrenocortical axis, increasing the hypothalamic secretion of corticotrophin-releasing hormone and responsiveness of the anterior pituitary release of corticotropin and adrenal secretion of cortisol.[38] A recent case-control study[39] of 183 subjects with metabolic syndrome demonstrating neurohumoral activation associated with chronic environmental stress further implicates a neurohumoral pathway as a common causal mechanism and potential target. Our results, demonstrating beneficial physiological effects of TM in the absence of effects on psychosocial variables, suggest that TM may modulate response to stress rather than alter the stress itself, similar to the physiological impact of exercise conditioning.

We did not observe group differences in the outcome variables of peripheral endothelial function, suggesting a lack of TM efficacy on this physiological variable. However, given our blood pressure and insulin resistance results, which should have contributed to improved endothelial function,[40,41] it is possible that other factors may have contributed to these negative results. The high prevalence of statin use and near-optimal low-density lipoprotein cholesterol levels may have precluded any incremental TM benefit via the neurohumoral-inflammatory pathways. Indeed, our mean high-sensitivity C-reactive

protein measure was relatively low for a CHD cohort and demonstrated no differences in response to the intervention. Although a significant effect was observed in HRV as hypothesized, this may have been minimized by the HE group's physical activity improvement because of the strong role exercise conditioning plays in cardiac autonomic nervous system tone.

The present study results add to those of previous randomized trials using TM for reduction of blood pressure. Although earlier meta-analyses questioned the efficacy of relaxation therapy[42] in treating hypertension, a more recent meta-analysis[43] concluded that individualized cognitive-behavioral approaches were comparable in magnitude to drug treatment effects in reducing blood pressure. A small trial demonstrated significant reductions in medication requirements in 39 hypertensive patients randomized to a 6-week multicomponent cognitive-behavioral intervention that included temperature biofeedback, progressive muscle relaxation, and therapy for stress and anger management.[44] Specific to TM, previous randomized trials[10-14] demonstrated decreased systolic and diastolic blood pressure compared with controls in sample sizes of 35 to 157 hypertensive and prehypertensive subjects. Our results are consistent with this body of literature, particularly with regard to nonhypertensive and prehypertensive subjects, because our CHD group did not have elevated mean blood pressure at study entry and only half had a history of hypertension.

Additional studies have examined the impact of stress management techniques on CHD outcomes. Although a number of psychological and group support trials[45] have not consistently demonstrated benefit for CHD outcomes such as nonfatal myocardial infarction and death, one study[46] that used specific mind-body techniques has demonstrated promising results. Pooled data from 2 published randomized controlled trials that compared the effects of mind-body interventions (including TM, mindfulness meditation, relaxation response, HE, and usual care) on blood pressure demonstrated adjusted relative hazard rates for TM compared with the control intervention of 0.77 (P=.04) for all-cause mortality and 0.70 (P=.045) for cardiovascular mortality.[47,48] A recent prospective trial by Blumenthal and coworkers[49] found that a multimodality psychological intervention in CHD patients had fewer recurrent coronary events at 5-year follow-up compared with those receiving usual care. Prospective trials performed with an adequate sample size are needed to address this issue.

Limitations of this trial included its relatively small size and short duration, which may have minimized the intervention effects. The patient population may not be representative of the general CHD population owing to the relatively low levels of low-density lipoprotein cholesterol and high physical activity levels. We used an indirect measure of insulin resistance (HOMA) that is increasingly being used as an outcome in clinical trials[50,51]; however, our results may have underestimated our effects. We did not perform ambulatory blood pressure monitoring and cannot exclude the possibility that the TM was effective only for reducing clinic blood pressure measures, although this is unlikely owing to previous work demonstrating efficacy (P=.04).[13] We did not measure waist circumference, and this limits our ability to assess the metabolic syndrome. Our self-reported psychosocial stress measures may have been insensitive to change. Our subgroup analyses were underpowered to test specific hypotheses in diabetic subjects, women, and the elderly (older than 75 years).

CONCLUSIONS

The present trial results demonstrate that 16 weeks of TM significantly reduces the adjusted blood pressure and insulin resistance components of the metabolic syndrome and has a positive impact on cardiac autonomic tone in subjects with stable, optimally managed CHD. These results suggest that neurohumoral pathways may be mechanistically involved in the metabolic syndrome. Our findings also suggest that interventions that target neurohumoral pathways, especially via meditation or related techniques, may be beneficial for CHD reduction and should be tested in larger, more adequately powered clinical trials.

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