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Clinical and Pre-clinical Applications of the Transcendental Meditation Program® in the Prevention and Treatment of Essential Hypertension and Cardiovascular Disease in Youth and Adults

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Abstract

Acute and chronic environmental and psychosocial stress contributes to the pathogenesis and progression of cardiovascular diseases (CVD). Stress reduction via Transcendental Meditation (TM)® has been shown to lower blood pressure (BP) levels and reduce CVD risk in adults and adolescents. This article reviews recent findings indicating a beneficial BP-lowering impact of TM in hypertensive adults at rest and in pre-hypertensive adolescents at rest, during acute laboratory stress and during normal daily activity. These findings have important implications for inclusion of TM in efforts to prevent and treat cardiovascular diseases and its clinical consequences.

INTRODUCTION

Cardiovascular disease (CVD) afflicts over 70 million Americans. It is the leading cause of death in the US, killing 927,444 Americans in 2002 and costing an estimated \$393 billion in 2005 [1]. Like most other diseases, CVD is multi-factorial in nature. Well-established preventable CVD risk factors include elevated serum cholesterol levels [2], high blood pressure (BP) [3], smoking [4], psychological distress/angry temperament [5], metabolic syndrome [6], obesity [7], stress [8] and physical inactivity [9]. Exposure to CVD risk factors during childhood and adolescence has been associated with the development of atherosclerosis later in life [10,11]. These risk factors, all modifiable, can be greatly benefitted by changes in lifestyle [12].

Environmental and psychosocial stress has been thought to play a significant role in the development of essential hypertension (EH) by acting through both acute and long-term BP control mechanisms [13,14]. Stress is defined as a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in physiological changes that, over time, may place the individual at risk for disease development [15]. The biobehavioral model of stress-induced hypertension depicted in Fig. 1 incorporates both the acute phase of the stress response, which results in a rapid BP increase, and the chronic phase of the stress response which acts to maintain elevated BP levels as long as physiologically needed to

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maintain homeostasis. Chronic sympathetic nervous system (SNS) activation has been linked to EH [16]. Stress has been hypothesized as contributing to the development of EH and CVD *via* a pathway of exaggerated cardiovascular reactivity [13,14,17]. The acute phase of the stress response involves complex neuroendocrine changes characterized by increased sympathetic activation [18]. Animal and human studies have demonstrated that exposure to chronic and acute stress may augment SNS activity resulting in increased levels of catecholamines including norepinephrine (NE) [19]. This results in a rapid rise in BP predominantly due to increased vasoconstriction [20], which increases total peripheral resistance (TPR) [21].

TREATMENT AND PREVENTION OF CVD THROUGH STRESS REDUCTION

Exposure to stress results in SNS-mediated increases in BP to cope with the immediate need for an increased blood supply to the brain and body. It is well established that the SNS activation in turn activates the renin-angiotensin-aldosterone system (RAAS), which includes release of the potent vasoconstrictive hormone, angiotensin II, which contributes to the acute rise in BP [19]. This response pattern is associated with concomitant increases in cardiac and vascular wall tension and intravascular shear stress that over time contribute to early vascular and ventricular remodeling which eventually lead to EH [13,14].

The recurrent and/or sustained exaggerated increases in BP responses to stress are associated with concomitant increases in cardiac and vascular wall tension [22,23]. It is hypothesized that over time this leads to secondary CV structural adaptation, that is, vascular and ventricular remodeling to help normalize wall tension [18,22,24]. An early sign of ventricular remodeling is increased left ventricular mass (LVM) which over time may lead to left ventricular hypertrophy (LVH), the strongest predictor of CV morbidity and mortality, other than advancing age [25–27]. Research findings have shown that BP reactivity in youth predicts LVH [28,29]. Importantly, changes in ventricular functioning that may occur concomitant with or prior to ventricular remodeling include increased resting heart rate (HR).

An individual's acute cardiovascular responses to stress are moderated by numerous psychological/lifestyle factors. For example, anger and hostility have been shown to be related to CV reactivity and a wide range of physical health problems including EH and CVD [30–35]. Similarly, coping styles (i.e., anger suppression, anger expression), perceived environmental stress (i.e., general stress levels, stressful life events, unfair treatment), and coping resources (e.g., family functioning, social support, stress reduction skills) are implicated in pathway. These variables have been associated with resting BP and/or CV reactivity in adolescents and/or young adults [36–40].

Although not entirely consistent [41], several prospective studies observed that BP reactivity predicts hypertension [42–45]. Exaggerated CV reactivity to stress has been hypothesized [13,14,17] as playing a particularly significant role in the development of EH due to exposure to both chronic and acute psychosocial and environmental stress (e.g., verbal/physical conflict with law/authority figures or family members, racism, inadequate economic resources, social disorganization, lower education and occupational status) [46–48]. Over the past decade pediatric studies found exaggerated BP reactivity to laboratory behavioral stressors is an independent predictor of increases in measures of pre-clinical CVD [49]. Increased peripheral vasoconstriction (i.e., TPR) has been implicated as playing an important role in the early development of EH [50]. Importantly, enhanced TPR is frequently the underlying hemodynamic mechanism responsible [51–53].

A functional measure of vascular remodeling is called diminished endothelium-dependent arterial dilation (EDAD) to reactive hyperemia [54]. Diminished EDAD is an index of

endothelial dysfunction, a relatively early event in the pathogenesis of CVD [55]. In youth and adults, decreased EDAD of femoral or brachial arteries to reactive hyperemia has been associated with elevated resting BP, smoking, hypercholesterolemia, CVD and EH [54–56]. Exaggerated SBP and/or TPR reactivity to acute stress has been found to be associated with diminished EDAD in normotensive youth and adults [57–59]. Collectively, these morphological and functional alterations in vascular and ventricular function lead to elevations in resting TPR and BP, which further lead to increases in left ventricular mass index and BP reactivity. A self-perpetuating cycle ensues which contributes to the pathogenesis of EH [21].

Evidence for the efficacy of certain nonpharmacologic approaches to preventing and controlling EH is strong [60]. Clinical research, primarily in adults, has shown behavioral interventions to have great promise in reducing BP levels, improving stress-related coping skills, and alleviating psychosocial distress. The benefits of psychosocial-behavioral interventions with respect to hypertension and CHD have been demonstrated in a number of trials in adults [61,62]. Stress reduction programs include those involving meditation, cognitive behavioral skills training, yoga and muscle relaxation. This review is limited to examining applications of the Transcendental Meditation (TM) program in prevention and treatment of EH and CVD.

There are several significant and unique aspects of the findings contained in this review. First and foremost is the wide range of subject populations, i.e., older and younger Caucasian Americans (CAs) and African Americans (AAs). The research endeavor with TM is among the few to extend behavioral stress reduction research to the adolescent population. Studies in youth are important for at least three reasons. (1) Such studies examine the effectiveness of a non-pharmacological therapy on BP reduction prior to the potentially confounding influences of sustained elevated BP that adversely affects the functioning of the organ systems later on in life [63]. (2) Epidemiological studies indicate that BP percentile rankings for age and sex tend to track from late childhood through adolescence into adulthood [64–66]. As such it is important to study individuals at a time when preventive strategies may still be effective prior to development of pathology. (3) Until now, the prevention of EH and CVD has not been a high priority in pediatric patients. As a result, little is known about the factors underlying pediatric EH. Therefore, given that the incidence of EH is increasing at an alarming rate, the prevention of EH and its consequences in the pediatric population has become an important area of investigation. Prevention of EH prior to the onset of target organ damage has been shown to be highly cost-effective [67].

The importance of the findings of this review lie in the concept that wide implementation of a non-pharmacological BP-reducing intervention could potentially have an enormous impact on public health. Even a small downward shift in the distribution of BP in the youth of a few mm Hg could substantially reduce the incidence of EH and related CVD [68]. Such decreases in youth and adolescents with elevated BP, if maintained over time, may potentially decrease long-term risk for hypertension [69]. The results of this review will provide insight into what has now become a very timely and important issue.

THE TRANSCENDENTAL MEDITATION TECHNIQUE (TM)

Chronic environmental stress is not easily altered. However, our model proposes that the effects of stress can be ameliorated *via* behavioral stress reduction, i.e., changing how the individual responds to stressors to reduce their negative impact on health. One approach which has been found to be particularly fruitful includes the Transcendental Meditation (TM) program.

The TM program requires no change in personal belief, religious or philosophical orientations and is easily learned by adults and adolescents [70]. TM is a simple mental technique that is learned over a standard seven-step course and practiced twenty minutes twice a day. Over 600 studies from over 210 universities and research institutions in 33 countries evaluating its effects have been published since 1970 [71–73]. Research evidence reviewed below indicates that it benefits many of the risk factors that contribute to CVD.

PART 1: PREVENTION: BLOOD PRESSURE REDUCTION STUDIES IN YOUTH

Hypertension is no longer considered an adult disease [69]. Blood pressure (BP) levels ‘track’ relative to peers from late childhood onward [74]. These levels may predict hypertension in young adulthood [74,75]. Children in the highest BP quintile are at greater risk to develop EH in early adulthood [74,76]. The incidence of hypertension has risen dramatically in recent years among youth [69], increasing as much as sevenfold among minority populations including African Americans (AAs) in which rates are now estimated at 5–12% [77]. These rates in adolescents are expected to increase together with increases in obesity [78].

CVD ranks as the number two cause of death in children under 15 [1]. In 1997, the National Institutes of Health announced an initiative for pediatric intervention studies for primary prevention of cardiovascular disease (CVD), which may benefit overall health and well-being, and reduce healthcare costs over the life span [79]. However, non-pharmacological interventions (e.g., electrolyte supplementation, diet, physical activity) have met with mixed results, with studies finding minimal to no effect upon BP in normotensive youth [75,80]. Sixth Joint National committee Report (JNC-6) failed to support the use of relaxation therapies for the treatment or prevention of hypertension [81], although a TM study was cited as having lowered BP at 3 months [82]. Furthermore, JNC-7 made no mention of relaxation therapies or meditation as a lifestyle modification option to manage hypertension, but rather emphasized weight and sodium reduction, adopting the ‘DASH’ diet, increasing physical activity and moderating alcohol [83]. The omission of relaxation/meditation options for lowering blood pressure in JNC-7 provides impetus for the present review, particularly since JNC-6 cited a TM study. Those with normal (pre-hypertensive) and optimal BP are encouraged to make lifestyle modifications to further reduce their risk of developing CVD [83]. In view of the recommendation of JNC-7 that health-promoting lifestyle modifications be implemented well before BP reaches the “hypertension” range, this review examining effectiveness of a lifestyle technique on BP lowering is highly relevant [83].

IMPACT OF TM ON RESTING BP AND BP REACTIVITY IN HIGH SCHOOL STUDENTS

Studies examining the impact of TM on BP in youth have been conducted by the Georgia Prevention Institute of the Medical College of Georgia. An 8-week pilot study examined resting BP and BP reactivity in adolescents with high normal BP [84]. Thirty-five adolescents (ages 15–18 years) with resting systolic blood pressure between the 85th to 95th percentile for their age, height and gender on 3 consecutive occasions, were randomly assigned to either TM (n=17) or health education control (CTL, n=18) groups. The groups did not differ on anthropomorphic, demographic, or pretest hemodynamic variables. The CTL group received lifestyle education sessions based on NIH guidelines on lowering BP through weight loss, diet and increasing physical activity. The TM group engaged in 15-min meditation sessions twice each day for 2 months including sessions during the school lunch break. Subjects’ cardiovascular function (BP, heart rate, and cardiac output) were measured

at minutes 10, 12 and 14 of supine rest and in reaction to a behavioral stressor (simulated car driving) and a social stressor (interview about a stressful event) every minute during the 10-minute stressor period. Assessors were blinded with respect to treatment status. After a two-month TM intervention, subjects were retested on the same protocol. The TM group exhibited a 4.8 mm Hg decrease in resting systolic BP (SBP) ($p=.03$) from pre- to 2 month post-intervention, compared to an increase of 2.6 mm Hg in the CTL group. The TM group also exhibited greater decreases from pre- to post-intervention SBP, heart rate and cardiac output reactivity ($p's<.03$) to the car driving stressor, and in SBP reactivity ($p=.03$) to the social stressor interview compared to the CTL group. These findings are important in consideration of TM's effects on hypertension because exaggerated cardiovascular reactivity to chronic stress may detrimentally impact on cardiovascular structure and function, contributing to hypertension and coronary heart disease [23,85].

AMBULATORY BP MONITORING

Ambulatory BP monitoring (ABPM) has been shown to improve prediction of hypertensive complications, be relatively free of placebo effects, highly reproducible and sensitive to small changes in average BP [86]. Multiple readings obtained over 24 hours yield a more reliable measure of overall daytime BP while white coat effects are eliminated [87]. This methodology facilitates observing real-life (at school and at home) BP, assessing the generalization of treatment effects in out-of-laboratory situations [88]. Reproducibility of ambulatory results have been validated in youth [89,90]. Findings in youth have indicated that ambulatory SBP measures are stable across periods of time varying from 1 to 4 years [91]. As compared to measures observed in a controlled laboratory environment, ambulatory BP measures cannot be influenced by laboratory evaluation personnel. Ambulatory BP monitoring has been recommended by JNC --6 and WHO for high reliability due to the 24-hour time series of BP measurements in the natural environment [92]. This approach is free from assessor blinding issues as the monitors can be programmed to measure BP automatically for many measurements during 24 hours. Blinding status becomes a non-issue since edits and calculations are performed automatically by the monitor software and the ABP monitor's computational programs are run without knowledge of group identification. The results are downloaded directly to computer storage from where daytime and nighttime means are used in the analyses [93]. This approach overcomes problems arising in studies that measure BP a few times in the physician's office on one day.

IMPACT OF TM ON AMBULATORY BP IN YOUTH

A 16-week random assignment intervention study was conducted with 156 AAs (mean age=16.2 yrs) with high normal SBP (pre-hypertensive, 85th to 95th percentile for their age group i.e., 129.2/75.3 mm Hg) [93]. Subjects were identified *via* BP screening conducted in the schools and were assigned to TM or CTL following pre-testing. On school days the TM group meditated for 15 minutes each day at school under the daily supervision of a certified TM instructor. On weekends and after school subjects practiced unsupervised at home. Average self reported compliance with TM at home was 75.9%. The CTL group participated in 15-minute cardiovascular health education sessions daily on school days. Ambulatory 24-hr BP measures were recorded at pretest, 2- and 4-month posttests, and 4-month follow-up. The study found decreased daytime SBP ($p=.04$) and diastolic BP (DBP) ($p=.06$) in the TM group compared to controls by approximately 4 mm Hg over the four-month intervention period, with a similar SBP decrease maintained at 4 months follow-up [93].

Potential cross-contamination might have existed between the groups if the control and TM subjects were in the same school at the same time. However, interventions (TM and control)

were provided separately to all schools over the study period to counterbalance the effect of school environment over the entire study.

IMPACT OF TM ON VASCULAR FUNCTION IN YOUTH

Diminished endothelium-dependent vasodilation to reactive hyperemia (EDAD) is an index of endothelial dysfunction. In youth and adults, decreased EDAD of femoral or brachial arteries to reactive hyperemia has been associated with risk factors for EH and CVD. The above BP study also determined the impact of TM on EDAD in adolescents with high normal blood pressure. 108 AA adolescents (age 16.2 ± 1.3 years) with high normal systolic blood pressure, were randomly assigned to either 4-month TM or health education control groups. Echocardiographically-derived measures of subjects' EDAD data were collected at pre-, post-4-month intervention and at 4-month follow up. The subject's right brachial artery was scanned in longitudinal section using a Hewlett-Packard 5500 with a 7.5 MHz ultrasound vascular transducer for 2 minutes following 4 minutes of arterial occlusion, induced by inflating a BP cuff to 200 mmHg. EDAD was calculated as the percent change from the baseline diameter to the maximum post cuff release diameter. The findings indicated that the TM group exhibited a significant increase in percent change in EDAD adjusted for pre-occlusion arterial diameter compared to the CTL group from pre-intervention to 4 month follow-up ($+2.56\%$ vs. -0.53% , $p < .05$). Significant improvement in EDAD suggests improved vascular function in the TM group compared to CTL in AA adolescents at risk. This finding was viewed as having the highest potential to change clinical practice from the perspective of treatment [94].

The TM program has a side-benefit that through daily practice, skill in managing CVD risk factors eventually leads to reduction in hypertension and CVD. By enhancing skill in stress reduction, one would be less likely to develop hypertension and subsequent health impairments later in life. Substantial benefits could be gained from an empirically validated program that would improve stress reduction skills. Few empirically validated BP-lowering programs are currently available for delivery to the public on a wide basis. Training of TM in childhood, if practice is continued over the long term, may have a beneficial impact upon hypertension risk and related health problems. Thus, the consequences and related economic costs of hypertension may be beneficially impacted if a cardio-protective technique such as TM is made available for youth and becomes a health promoting lifestyle behavior continued throughout life [95].

In summary, the findings indicate that TM has a beneficial effect upon resting and ambulatory BP, CV reactivity to behavioral stress and ventricular function. Whether decreased SNS activity, decreased CV reactivity and improved renal function are physiological pathways linking TM with improved BP control *via* improved ventricular and vascular function is unknown and requires further study. Most importantly, studies are needed to determine whether different types of behavioral stress reduction programs such as TM, will improve SBP *via* decreased anger and hostility and improved neurohormonal, renal, vascular and ventricular function, particularly during stress in those at particular risk for development of EH.

PART 2: TREATMENT OF CARDIOVASCULAR RISK FACTORS IN ADULTS

Recommendations of BP-lowering by JNC-7 [83] reflects the inescapable epidemiological fact that BP-related disease cannot be minimized only by treating those with clinical hypertension. Indeed, safe and effective measures to achieve small but significant reductions in BP across entire populations could have a far greater impact in reducing CVD than strategies targeting only higher risk patients. As recommended by JNC-7, the first choice for

such measures should be lifestyle/non-pharmacological. TM's effects in reducing BP in both hypertensive and pre-hypertensive individuals [82,84,93,96–100] coupled with its additional benefits for health-related behaviors and well-being [99,101,102], could be extremely valuable as part of a population strategy for CVD prevention.

Jevning *et al.* reviewed findings on the impact of TM on acute changes in oxygen consumption, respiration, circulation, tissue metabolism, endocrine, neurotransmitter and autonomic effects, EEG, evoked potential and sensory and motor responses, concluding that the impact of TM is as an integrated response [103]. The review discusses mechanics by which TM reduces baseline levels of stress hormones and suggests that TM provides the physiological basis for a more adaptive response to stress facilitated by a unique deep metabolic rest during which the body's homeostatic mechanism can normalize malfunctions in the system. The review highlights the need for further research to distinguish TM from other forms of relaxation or stress reduction.

META-ANALYSIS ON PHYSIOLOGICAL EFFECTS AND REVIEWS OF PSYCHOLOGICAL AND PHYSIOLOGICAL MECHANISMS

A meta-analysis of 32 physiological studies by Dillbeck and Orme-Johnson [104] found that TM produces deeper rest than ordinary relaxation, as indicated by greater increases in basal skin resistance, greater decreases in respiration rate, and greater decreases in plasma lactate, a biochemical stress marker. The study also showed that meditators have lower baseline levels of stress outside of the meditation period as indicated by lower measures of sympathetic arousal, (heart rate, respiration rate, spontaneous skin resistance responses, plasma lactate), and finds the TM technique to be more effective than clinically derived methods in reducing several CVD risk factors, i.e., blood pressure [104].

A well-presented model of pathophysiological mechanisms linking psychosocial stress to CVD events is presented by Bairey Merz *et al.* [105]. Links between psychosocial stress and atherosclerosis, endothelial function, plaque rupture, thrombosis and arrhythmias are presented. Part 2 of this series discusses the effectiveness of TM in treatment and prevention of CVD risk factors including BP, lipids and cholesterol, tobacco and CV reactivity to stress, with helpful tables summarizing the findings [106]. The review discusses TM's impact on psychological and physiological mechanisms, and highlights reductions in CVD morbidity and mortality, including regression of atherosclerosis, left ventricular hypertrophy and myocardial ischemia.

Part 3 of this series examines clinical and policy implications of research on TM, reviews TM's impact on medical care utilization, and provides recommendations for health insurance claims and physician reimbursements [107]. The nature and effects of TM which included its origin and standardized instruction, and compliance issues are discussed. The article highlights the need for education of public and health care professionals of TM's benefits and gives policy recommendations with regard to issues such as services, provision, certification, licensure issues, and reimbursement. Evidence supporting TM for primary and secondary CVD prevention are reviewed and the addition of TM instruction to the health care system is recommended. Concerns related to feasibility of implementation of TM in large-scale settings (e.g., schools, communities, etc.) and availability of specially trained TM teachers were not addressed.

IMPACT ON HYPERTENSION

The efficacy of conventional drug therapy in preventing the most frequent complication of hypertension, i.e., CVD, is less than perfect. For example, anti-hypertensive drug therapy

has been associated with tolerability of adverse side effects [108], impaired quality of life concerns [109], and cost effectiveness [110]. However, opinion is mixed regarding patient compliance and BP control [111], and some propound that the relationship has not yet been well established [112]. For these and other reasons the other reasons JNC-7, the National High Blood Pressure Education Program, and the Working Group in Hypertension have recommended non-drug lifestyle modification approaches as first-line definitive or adjunctive treatment for hypertension [83]. Given the inconsistencies that lifestyle interventions have upon BP control and the potential role of psychosocial stress in the development of EH, stress reduction has been shown to be beneficial in the reduction of BP. Adult long-term practitioners of TM have significantly lower BP compared with age group-based population norms [113]. In recent years, well controlled randomized clinical trials (RCT) have been conducted to examine the BP-lowering impact of stress reduction *via* TM in adults as well as adolescents. Studies with adults have been extensively reviewed previously and will be briefly summarized below [96,106, 107,114–116].

Research on TM and hypertension in adults originated at a number of independent universities, starting in the early 1970's. Studies with mild and moderate hypertensives were carried out at Harvard Medical School [117], College of Medicine, University of Cincinnati, Cardiovascular Center [118], and Medical College of Allahabad, India [119]. These studies used multiple baseline measures to control for adaptation effects. The group means at baseline of the studies ranged from SBP/DBP 150/94 mm Hg [117] to 157/102 mm Hg [119]. Collectively, these studies [117–119] reported that after a mean of 6 months of TM practice, SBP/DBP decreased by a mean of $-12.6/-8.8$ mm Hg. Recently larger and better-controlled randomized clinical trials [82,84,93,96–100] have corroborated early findings that TM has a beneficial effect of BP.

A safeguard against potential researcher bias built into randomized studies was that BP data were collected by independent personnel at independent institutions. Studies have been conducted by authors associated with Maharishi University of Management or who practiced TM, in association with independent collaborators from Harvard University and University of Maryland [99], West Oakland Health Center, University of Arkansas, and Haight-Ashbury Free Clinic [97], University of Iowa Hospitals and Clinics [98], Morehouse School of Medicine, Lake Merritt Heart Care, Haight-Ashbury and West Oakland Health Clinics, and University of Michigan [100].

Data were collected in homes for the elderly in the Boston area [99], West Oakland Health Care Center, an inner city, primary care, community health clinic in Oakland, California [82,96,97,100], Clinical Research Center of the University of Iowa Hospitals and Clinics [98]. These studies were funded by grants from the National Institute of Mental Health [99], National Institutes of Health, including the National Heart, Lung and Blood Institute [98,100,120], the Retirement Research Foundation and the Lancaster Foundation [97].

In the first randomized clinical trial (RCT) on TM and blood pressure, Alexander *et al.* [99] studied 73 elderly subjects in the Boston area. The mean age was 80.7 years, and subjects were randomly assigned to the TM program or to inventions designed to match the TM program for contact time with the teacher and expectation-fostering features, or to a third no-treatment control. The active control groups were mindfulness training, which “involved both a structured word-production task and an unstructured creative mental activity task”, and a TM-analog mental relaxation technique. Posttest levels of systolic SBP, adjusting for pretest levels indicated that SBP for the TM group was 4.9 mm Hg lower than mindfulness, 19.6 mm Hg lower than mental relaxation, and 9.9 mm Hg lower than no-treatment. Planned comparison for this pattern of results was significant at $p < .01$.

In a later RCT on TM and blood pressure, Schneider *et al.* [97] randomly assigned 127 older African Americans to either TM, Progressive Muscle Relaxation (PMR) or a health education program consisting of dietary and exercise recommendations (HE). Multiple baseline measurements were taken, and after three months of intervention, the unadjusted change in SBP in mm Hg was -10.4 for TM, -4.0 for PMR, and -1.5 for HE. The unadjusted change in DBP in mm Hg was -5.7 for TM, -2.1 for PMR, and $+6$ for HE. Controlling for age produced significant results for TM on SBP when compared to PMR ($p<.025$) or HE ($p<.0005$), and for DBP, TM compared to PMR ($p<.05$) or HE ($p<.00005$). TM appears to be more efficacious for those who are not on medication, but also simultaneously decreases BP and use of anti-hypertension medication [120], and has been found to reduce the reliance on and desire for drugs in general [121]. A separate subgroup analyses by sex was published by Alexander *et al.* suggested efficacy of TM for treating hypertension in patients in high as well as low risk categories for six hypertension-related measures of risk: obesity, alcohol use, psychosocial stress, dietary sodium-to-potassium ratio, physical inactivity, and presence of multiple risks [82].

In the third RCT on TM and blood pressure, Wenneberg *et al.* [98] randomly assigned 66 normotensive 18–34 year old men (mean BP 124.8/70.7 mm Hg) to either TM or to an active control condition modeled after the standard TM course to control for expectancy, instructor attention, and daily time commitment. After four months of treatment, ambulatory DBP decreased by 8.8 mm Hg in high-compliance TM subjects compared to an increase of 2.3 mm Hg in high-compliance controls, but did not change significantly for SBP. A possible interpretation is that TM is effective, but obviously only for those who practice it. The findings raise the practical question of which patients are willing to learn the technique and continue practicing it—a different issue from whether TM is effective or not.

In the fourth RCT on TM and blood pressure, Schneider *et al.* [120] collaborated with the Haight-Ashbury Free Medical Clinic supported by an NIH grant extending the earlier three-month design [97] to one-year. The study randomly assigned 150 hypertensive African Americans (mean age 49 years; mean 142/95 mm Hg) to TM, Progressive Muscle Relaxation (PMR), or Health Education (HE). Three baseline measurements were taken during each of five sessions spread over one month, and the mean of the 4th and 5th sessions were used as the baseline. The mean change over the year-long intervention for TM was a decrease in SBP/DBP by $-3.1/-5.7$ mm Hg compared to $-0.5/-2.9$ mm Hg for PMR or HE, (p 's <0.1 for SBP, p 's <0.01 , for DBP). The study found significant within-group BP reductions for TM by the third month, whereas the changes in the other groups did not manifest until after 6 months, providing a longer sustained period of lowered BP for the TM group. The TM group also decreased the use of anti-hypertensive medication relative to PMR ($p<.001$) and HE ($p<.09$, trend).

STRESS REDUCTION, CORTISOL AND CVD RISK

Stress affects health adversely through limiting or distorting the normal functioning of adaptive mechanisms [95]. Modifying response to stress has been found to reduce cardiac events [122,123]. TM habituates the nervous system to maintain a more restfully alert resting baseline outside the TM practice [124]. This is indicated by the lower baseline levels outside TM of autonomic measures such as heart and respiration rates [124]. It has been suggested that TM practice facilitates maintenance of a more efficient style of functioning which conserves more energy during non-stressful periods to utilize for coping with stress [115]. In support of this, MacLean *et al.* reported that TM practice develops a stronger, more adaptive autonomic response to the challenges of stressors, as indicated by improved heart rate, skin resistance, and cortisol responses [125,126].

Cortisol, when produced at appropriate levels, effectively modulates various acute responses to stress [95]. However, chronic stress causes cortisol overproduction, resulting in damaging effects. There is evidence that elevated cortisol levels or impaired cortisol regulation increases atherosclerosis [127], hypertension [128], cancer [129], obesity [130], osteoporosis [131], immunodeficiency [132], hyperlipidemia [133,134], depression [135], some anxiety [136] and aggression-related disorders, such as drug abuse and other addictive disorders [137]. TM practice has been shown to produce a healthy cortisol profile of lower baseline levels and a more robust cortisol response to acute stress. A 27% decline in cortisol concentration during TM reported in studies by Jevning *et al.* is consistent with complete inhibition of cortisol excretion [138,139]. These findings suggest that adaptive efficiency is a concept that captures TM's many effects. The strengthening effect of the TM program on the physiology may help to attenuate the negative impact of environmental stressors.

DECREASED SERUM CHOLESTEROL LEVELS

One of the CVD risk factors that normalizes through regular TM practice is serum cholesterol levels. A controlled longitudinal study over an 11-month period found that the TM program reduces serum cholesterol levels. Recent evidence suggests that oxidant stress impacts several functions of the endothelium, including modulation of vasomotor tone [140]. Related to this, 15% lower serum levels of lipid peroxides were found in a study of healthy normotensive TM practitioners compared with matched controls ($p < .03$). The mechanism for TM's impact on cholesterol levels is unclear but may involve improved lipid metabolism or better dietary choices, or both [141].

EFFECTS ON TOBACCO AND ALCOHOL USAGE

Cigarette smoking continues to be a major health hazard, and contributes significantly to cardiovascular morbidity and mortality [142]. Research has established a solid relationship between drinking and higher BP [143] and CVD [144]. Effects of TM on tobacco, alcohol, and drug abuse have been reviewed in a number of groups, ranging from the general population to incarcerated drug offenders [145]. A wide range of evidence suggests that the restorative rest produced by TM normalizes the neurochemical imbalances caused by substance abuse [146]. As a result, the physiological basis for craving is thought to decline, which is often accompanied by a decline in substance use [147]. A meta-analysis of 198 studies on behavioral techniques for reducing tobacco, alcohol, and drug consumption suggested that TM had substantially larger effect sizes in reducing harmful substance consumption than other techniques, including relaxation programs, therapeutic probation, pharmacological intervention, educational programs, and unconventional treatments (e.g., acupuncture) [121]. The TM studies also showed that patterns of abstinence were maintained for a longer time. A prospective study of 324 cigarette smokers found that 51% of those who reported full compliance with the TM practice quit smoking after two years, compared to 21% for both partial TM adherents and non-TM controls. The TM program gives no advice to quit smoking [70]. Rather, reduction in smoking is thought to be motivated by the increased sensitivity to the harmful effects of tobacco on the body [148].

ACUTE EFFECTS OF TM ON CV FUNCTION

Increased vasoconstriction has been implicated in the development of EH [50]. Decreased vascular resistance (total peripheral resistance, TPR) is associated with an increase in cardiac output [149]. The acute effect of TM upon CV function was examined in a group of 32 healthy middle aged adults (mean age = 46.7 ± 3.7 yrs) without any history of vascular dysfunction [150]. Long term TM practitioners (mean regular twice daily TM practice = 23.7 ± 5.2 years) were compared to a matched normotensive control group on CV function at rest and during 20 minutes of self-relaxation (eyes closed rest for control group versus TM).

The TM group exhibited greater decreases in SBP (-3.0 vs. $+2.1$ mmHg, $p<.04$) and TPR (-1.0 vs. $+0.3$ mmHg/L/min, $p<.03$) compared to self-relaxation in the control group. TPR decreased significantly during TM. Decreases in vasoconstrictive tone during TM may be the hemodynamic mechanism responsible for reduction of high BP over time. The results of this study provide a preliminary contribution to the understanding of the underlying hemodynamic mechanisms responsible for beneficial influence of TM upon cardiovascular risk factors.

DECREASED ANGINA PECTORIS AND CAROTID ATHEROSCLEROSIS

A controlled longitudinal study of angina pectoris reported that TM improved exercise tolerance, increased maximum workload, and delayed appearance of electrocardiographic abnormalities during exercise (delayed onset of ST segment depression) in heart patients after 1 year of TM practice [151]. In another study, TM was associated with reduced carotid atherosclerosis in hypertensive African-Americans (AAs) [152].

REDUCED CARDIOVASCULAR MORBIDITY

The results of two large field studies of Blue Cross/Blue Shield of Iowa insurance statistics reported markedly lower medical utilization for TM subjects. The first study examined a group of TM participants that increased in size from 694 to 2,119 over the five-year study period [153]. The TM group was compared to the Blue Cross norm groups comprised of approximately 600,000 members and to five other groups (combined $N=22,440$) selected by Blue Cross to be of comparable policies, size, and professional membership as the TM group. The TM group's rate of hospitalization for diseases of the heart and blood vessels was 87% lower than the norm. The overall admissions rate for all causes for the TM group was 55% lower than other groups. The TM group's average length of hospital stay was 4.5 days compared to 5.4 days for other groups, patient days per 1000 were 61% lower, and TM outpatient visits were 53% lower. Analysis by age categories showed approximately a 50% reduction in inpatient and outpatient admission rates for all causes for the younger TM groups, with even greater reductions of 68% and 74%, respectively, for TM practitioners over 40. Since CVD incidence increases with age, the findings of this study has profound implications for TM with regard to CVD prevention.

COST EFFECTIVENESS OF TM IN TREATING HYPERTENSION

As reviewed above, randomized studies suggest that TM reduces blood pressure in hypertension as effectively as do drug therapies. Cost-effectiveness of managing hypertension comparing TM with the five leading anti-hypertensive drugs was analyzed by Herron *et al.* [154] This cost-effectiveness comparison in 1996 dollars over a simulated 20-year treatment period reported that TM had the lowest present value cost, and the best health benefits. The study indicated that TM is a cost-effective treatment for hypertension with many side benefits.

CARDIOVASCULAR MORTALITY

Two random assignment studies found that the TM program decreased mortality rates from cardiovascular disease, as well as for death by all causes [155,156]. The first study was a 15-year follow-up of 87 subjects over 80 years old who had been randomly assigned to TM, mindfulness training (MF), mental relaxation (MR) and a no-treatment control (NT). In this study after 3 years survival for the TM patients was 100% compared lower rates for other groups [99]. After 16 years, mean survival time for CVD was higher, and all-cause mortality was significantly lower for the TM group compared to the other groups combined.

In a second study, mortality and cause of death were assessed from vital statistics over 8 years of follow-up on 109 older African American patients with mild hypertension (mean age 67 years) who had participated in a hypertension study [97]. Subjects were randomly assigned to two active stress reduction approaches—the TM program or progressive muscle relaxation (PMR)—or a health education control (EC) program for three months. The adjusted relative risk for CVD mortality of the TM group compared with EC was significantly reduced by 81%. The adjusted relative risk for all-cause mortality of the TM group compared with PMR showed a trend at 57% reduction in the analysis of the 3-month finishers. When patient data from the above two randomized controlled trials was combined in a post-hoc analysis [157], the TM group showed a 23% reduction in all cause mortality compared to combined controls, a 30% reduction in the rate of cardiovascular mortality and a 49% reduction in the rate of cancer mortality. These studies require replication in a larger study but collectively suggest that TM may offer benefit for reducing all-cause and CVD mortality.

If an effective, long-term non-pharmacological approach shown to reduce the incidence of EH and CVD could be applied on a widespread basis, the significance could hardly be underestimated. Recent epidemiologic studies have documented worrisome trends towards increasing BP and obesity levels in adolescents [158]. Since CVD risk factors have been shown to persist into adulthood, this may translate into a CVD epidemic in the future. Health care providers need to assume greater responsibility for the prevention, detection, and intervention relevant to CVD risk factors in adolescents [159]. The urgent need for both population-based and individual approaches to primary prevention of CVD beginning in childhood cannot be over-emphasized [160]. Adolescents should be empowered through education and skill development to assume increasing responsibility for their own health behaviors [161]. School-based interventions including stress reduction can improve the CVD risk profile of children and should be utilized as one means of early primary prevention of CVD [80].

In summary, TM is an easily learned, cost effective means of reducing resting and ambulatory blood pressure and CV reactivity, and improving ventricular function in adolescents at risk for hypertension. In adults with mild or moderate EH, TM decreases blood pressure, reduces the use of anti-hypertensive medication, decreases angina pectoris and carotid atherosclerosis. It markedly reduces medical care utilization for CVD, especially in older individuals, and it significantly decreases CVD and all-cause mortality. The mechanism of TM's effects appears to be through acute and longitudinal reductions in sympathetic tone and reactivity to stress. It decreases resting heart, respiratory rates and cortisol levels, improves CV function, and decreases stress-related risk factors, including serum cholesterol levels, and alcohol and tobacco use.

Considerable compelling evidence for the efficacy of TM as an approach to preventing and controlling EH and CVD risk has also been documented in extensive reviews [96,106,116,162]. Evidence presented offers a basis for public health policies and clinical approaches that can greatly affect the incidence and consequences of EH and CVD in the population at large [107]. The effective implementation of stress reduction depends to a large extent on the training and motivation of the health care administration. The support and involvement of health professionals, educators, community organizations, industry and government together is necessary to support the adoption of healthy lifestyles for our society for succeeding generations [163]. Intervention through stress reduction in youth and adults is suggested as a future direction for preventive cardiology.

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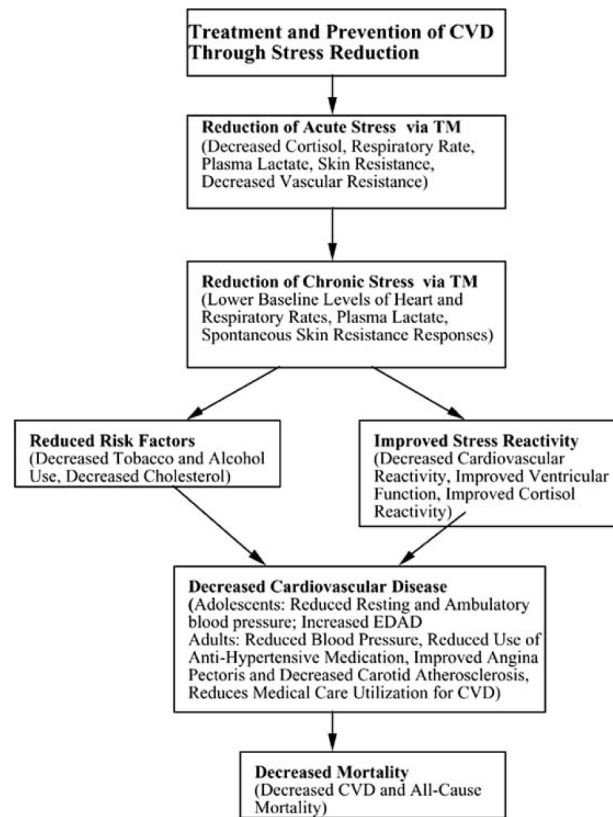


Fig. (1).

A model of the TM's effects on hypertension and CVD as reviewed in this paper is presented. Chronic environmental and psychosocial stress, and genetic predisposition, contribute to an increase in acute stress-induced SNS arousal resulting in increased neurohormonal activity and hypothalamic pituitary adrenocortical (HPA) axis dysregulation. Such changes result in greater BP responsivity to the stress, vasoconstriction and increased BP levels. Reduction of acute and chronic stress *via* TM reduces CVD risk factors and impacts on the SNS resulting in reduced BP reactivity to acute stress. Over time, due to decreased cardiovascular reactivity to acute events, there is reduced load upon the heart resulting in decreased BP levels, thereby helping to prevent early onset of EH [13].