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Original Article

Adhering to a Tai Chi Chuan Exercise Program Improves Vascular Resistance and Cardiac Function☆

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SUMMARY

Background: Cardiac function is an important predictor for life expectancy in elderly subjects. Tai Chi Chuan (TCC) is a generalized tolerable exercise for the aged population. The current study evaluated the effects of TCC on the vascular compliance and resistance as well as cardiac function of a general healthy elderly population.
Materials and methods: A total of 122 consecutive subjects were enrolled from the general population. Yang style TCC was practiced three times a week for 1 hour each session for a duration of 5 months. Subjects were categorized as "adherents" ($n = 33$) if they participated in >48 (80%) sessions, or as "non-adherents" ($n = 34$). Biochemistry data, including fasting glucose, serum cholesterol, triglycerides, uric acid, were recorded before and after the 5-month intervention. Hemodynamic variables, including vascular compliance, resistance, cardiac output, stroke volume, and left ventricular ejection fraction, were obtained before and after the program using a Dynapulse 200 M monitor.
Results: Serum triglyceride levels declined after TCC practice (the changes in triglycerides were −3.12 mg/dL and 18.8 mg/dL for the adherent and non-adherent groups, respectively; $p = 0.03$). Significant differences between the adherent and non-adherent groups existed in left ventricular contractility, cardiac output, cardiac index, stroke volume, and brachial artery compliance ($p < 0.01$; $p = 0.01$; $p < 0.01$; $p < 0.01$; $p = 0.02$, respectively).
Conclusion: A 5-month TCC intervention can have a favorable impact on some biochemical indices of cardiovascular risk. This intervention can also have favorable effects upon hemodynamic parameters. These findings indicate that TCC intervention may offer enhanced cardioprotective effects in the aged population.

1. Introduction

Tai Chi Chuan (TCC) is a unique exercise that has been practiced in China, Japan, Korea and other Asian countries for several hundred of years, particularly for the elderly population. However, its importance and benefits have been recognized only in recent years after a number of case–control studies and clinical trials[1,2]. TCC emphasizes the balance of the body and the mind, and is performed in a variety of ways, including the Chen, the Yang, the Wu, and the Sun styles[3]. The Yang style is the most popular, according to various studies. TCC is practiced in a semi-squat posture with a series of continual motions, balances, relaxations and slow deep breaths[4]. Despite its slow motion, it is considered to be a moderately intense form of aerobic exercise because it does not demand >55% of maximum oxygen intake[5], but equivalent in intensity to those recommended for the prevention of cardiovascular disease[6].

Cardiovascular disease (CVD) is clearly an important public health problem. Mortality due to CVD can be striking and unbearable to the family and relatives of the deceased person. Since 1992, mortality related to CVD has slightly decreased in Taiwan thanks to improved cardiac care, but hospitalization rates for CVD have significantly increased from 1996 to 2001[7]. In China, a recent study has reported that the rates of CVD mortality in Beijing increased by >50% in men and >27% in women from 1984 to 1999. These

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increases may be attributed to changes in lifestyle, including a substantial rise in cholesterol levels, dramatically less exercise, and even genetic factors[8–13].

Of all preventive methods, exercise is the core component for the cardiac rehabilitation of patients with CVD and is a major factor in improving one's well-being. Mind–body interventions, such as TCC, are complementary therapies that are frequently used. TCC is a reliable and tolerable exercise for all ages of patients and may offer some benefits for preventing or treating CVD. According to a recent review of the effects of TCC on CVD[14], it may lower blood pressure in patients with hypertension and prevent the incidence of stroke or congestive heart failure. However, the evidence about TCC for CVD is still scarce and there are no studies about TCC and its influence on cardiac function in a general population. A noninvasive technique has recently been developed that can measure isolated pressure and rates of pressure change (DynaPulset, Pulse Metric, San Diego, CA, USA). The technology has the potential to measure not only arterial pressure, but also structural properties, such as vascular compliance, cardiac output, and stroke volume[15].

In the current study, we applied the new technology for noninvasive measurements of changes in cardiac structural properties before and after TCC intervention. We also investigated whether adherence to the exercise had any influence on various cardiac performance parameters.

2. Materials and methods

2.1. Study population and design

One hundred and twenty-two consecutive elderly participants (age >50 years) free from hypertension, diabetes and hyperlipidemia were recruited from a Tai Chi club at Taipei City Hospital, Renai branch. All were community dwellers and led active lifestyles that consisted of regular exercise at least three times a week. Subjects were excluded if they had a history of significant cardiovascular, pulmonary, metabolic, musculoskeletal (e.g., joint fracture, or artificial joint replacement), renal or neurological (e.g., stroke, Parkinson's disease, dementia, or poor vision) disease. Eighty-three subjects completed both pre- and post-test measurements in a 5-month intervention program and were finally recruited. The subjects were predominantly female (70%), with a mean age of 62.3 years [standard deviation (SD) = 9.0]. The mean body mass index (BMI) of the subjects was 23.4 kg/m^2 and none of the participants was overweight. The participants were asked to take food ordinarily during the 5-month course.

Based on the recommendations of the American College of Sports Medicine that 80% of exercise attendance is required for significant outcomes to be found[16], 16 participants did not sign in regularly during the program and were dropped from the adherence analysis. Subjects were categorized as "adherent" ($n = 33$) if they participated in >48 sessions or as "non-adherent" ($n = 34$) if otherwise. The study was approved by the local institution committee, and the subjects gave their informed consent.

2.2. TCC Intervention

The TCC program consisted of 24 movements from the Yang styles (http://www.egreenway.com/taichichuan/short.htm#List), which are distinguished primarily as deep breathing accompanying the opening and closing of hands and the stepping forward and backward with weight transference[17]. Each session began with a warm-up exercise to prepare the body, and sessions ended with a cool-down exercise to release muscle tension and stiffness. Subjects in the program practiced at least three times a week for 1 hour each time. The entire intervention length was 5 months. Before starting the TCC program, certified TCC instructors trained with and ensured that each subject was familiar with a standard TCC program.

2.3. Baseline risk factor records

Data were collected by trained personnel according to standardized procedures. Blood pressure (BP) was measured in the right arm unless otherwise specified. Average systolic BP (SBP) and diastolic BP (DBP) were obtained. Sex was self-reported and age was calculated according to birth date. BMI was calculated as weight (kg) divided by height (m^2).

2.4. Laboratory assays

After fasting for 10–14 hours, subjects underwent venous blood sampling from an antecubital vein. Blood glucose and lipid profile, including total cholesterol, triglycerides, and low-density lipoprotein-cholesterol were measured using the autoanalyzer provided by Taipei Institute of Pathology. Biochemistry data, including C-reactive protein and uric acid levels, were also measured.

2.5. Measurements of vascular resistance and cardiac function

Our current study used the Dynapulse 200 M monitor (Pulse Metric, San Diego, CA, USA) to measure vascular resistance and compliance along with left ventricular (LV) contractility and stroke volume. The Dynapulse system used a noninvasive procedure to record and display oscillometric pressure waveform signals from the brachial artery (BA) using a conventional BP cuff wrapped around the upper arm. The procedure was similar to conventional BP measurement. A detailed description of the method has already been published[18,19]. In brief, this instrument employed pulse dynamic pattern recognition technology, whereby integration of the pulsation signal with measurements of isolated pressure and the rate of pressure change at the BA over time (dP/dt max) was used to determine the hemodynamic properties of the BA using a proprietary algorithm. Previous validation studies of the DynaPulse instrument have demonstrated a high correlation between compliance (from which distensibility was calculated) measured with cardiac catheterization and compliance derived by noninvasive means[18–20]. Hemodynamic measurements were taken in triplicate both before and after TCC intervention. Subjects rested for at least 5 minutes before measurements were taken. Waveforms for each patient were downloaded to a personal computer with device-specific software and then uploaded to a web-based analysis center (Dynapulse Analysis Center: http://www.dynapulse.com) for analysis of the tracings and the provision of a table with values for the hemodynamic parameters.

2.6. Statistical methods

SAS version 9.1 software (SAS Institute, Cary, NC, USA) was used for data analysis. Baseline characteristics, biochemistry data and cardiovascular parameters were calculated and presented with means and SD. Effects of all data after the 5-month TCC program were compared by Student's paired t test. Between-group (adherent and non-adherent group) data were compared using Student's unpaired t test for continuous data and a χ^2 test for categorical data. A value of $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

Of the 122 participants, 83 subjects with complete measurements of laboratory data were ultimately enrolled in the study. Most subjects were female (70%). Mean age of the subjects was 62.3 years (SD = 9.0). The mean BMI (23.4 kg/m^2) of the subjects was in the normal range according to the definition of obesity in a Taiwanese population (http://www.doh.gov.tw/CHT2006/DM/DM2_p01.aspx?class_no=25&now_fod_list_no=5912&level_no=2&doc_no=22602). None of the participants had a diagnosis of hypertension or diabetes mellitus.

3.2. Effects of the 5-month TCC exercise

After the 5-month TCC program was completed, we used a paired t test to estimate its effects. Overall, there were significant differences in weight, SBP and DBP, as well as serum fasting glucose levels for all the subjects after the exercise program. There were no significant differences observed in cholesterol, low-density lipoprotein and uric acid levels. Using the Dynapulse system, we estimated the cardiovascular parameters and found a significant difference after exercise in LV ejection, LV contractility, cardiac output, stroke volume index and systemic vascular resistance (SVR). The effects of the TCC program using variable entities are shown in Table 1.

3.3. Effects of adherence to TCC

The subjects were divided into two groups: adherents (who attended 80% of the TCC sessions) and non-adherents (who attended <80% of the sessions), to compare the effects of adherence to the TCC regimen. Baseline differences (before the exercise program) for the two groups are listed in Table 2. The adherents had a significantly higher attendance rate than the non-adherents ($p < 0.01$).

There was no significant difference observed in any of the anthropometric and biochemistry data between the two groups. After calculating the cardiovascular parameters using noninvasive methods, no significant differences of any kind were observed between the two groups before the exercise program began.

After the 5-month TCC exercise program intervention, the adherent group had significantly lower serum triglyceride levels, although differences in other biomarkers were insignificant. As we investigated the cardiovascular parameters, we noted the adherent group had much improved LV contractility, cardiac output, cardiac index, stroke volume, and SVR, than the non-adherent group (adherents vs. non-adherents, $p < 0.01$ vs. $p = 0.27$; $p < 0.01$ vs. $p = 0.70$; $p < 0.01$ vs. $p = 0.17$; $p < 0.01$ vs. $p = 0.17$; $p < 0.01$ vs. $p = 0.16$, respectively) (Table 3). However the BA compliance deteriorated significantly only in the adherent group after the program ($p < 0.01$ vs. $p = 0.55$) (Table 3).

Table 1
Effects on basic characteristics, biomarker and cardiovascular parameters after 5 months Tai-Chi Chuan exercise.

$n = 83$	Pre-test	Post-test	p^*
Basic characteristics			
Weight, kg	60.6 (10.5)	60.0 (10.5)	< 0.01
SBP, mmHg	134 (19.7)	126 (19.4)	< 0.01
DBP, mmHg	75.4 (10.7)	69.4 (10.7)	< 0.01
PP, mmHg	58.9 (14.7)	57.1 (13.2)	0.19
HR, beats/min	72.3 (9.8)	73.5 (9.3)	0.15
Biomarkers			
Fasting sugar, mg/dL	97.5 (8.29)	92.8 (7.80)	< 0.01
Cholesterol, mg/dL	196 (31.1)	198 (30.6)	0.47
Triglyceride, mg/dL	107 (45.3)	112 (49.3)	0.25
LDL-C, mg/dL	125 (29.1)	126 (29.1)	0.80
Uric acid	5.31 (1.21)	5.45 (1.31)	0.10
hs-CRP	0.16 (0.20)	0.14 (0.21)	0.57
Cardiovascular parameters			
LV ejection time, sec	0.283 (0.03)	0.280 (0.04)	0.03
LV dP/dt max, mmHg/sec	1220 (296)	1193 (282)	0.30
LV contractility, 1/sec	14.9 (1.97)	15.5 (2.05)	0.01
Cardiac output, L/min	4.61 (1.00)	4.80 (1.04)	0.02
Cardiac index, L/min/m^2	2.82 (0.53)	2.97 (0.56)	0.01
Stroke volume, mL	62.7 (8.94)	64.0 (9.77)	0.04
Stroke volume index, mL/m^2	38.5 (3.80)	39.5 (4.06)	0.01
SV compliance, mL/mmHg	1.11 (0.23)	1.16 (0.21)	0.03
SV resistance, dynes/sec/cm^5	1695 (345)	1521 (346)	< 0.01
BA compliance, mL/mmHg	0.057 (0.02)	0.055 (0.02)	0.14
BA distensibility, %/mmHg	5.68 (1.43)	5.80 (1.36)	0.45
BA resistance, kdynes/sec/cm^5	277 (119)	279 (108)	0.81

$^*p$ values that compared pre and post-test results were calculated with paired-sample t tests; BA = brachial artery; DBP = diastolic blood pressure; dP/dt max = isolated pressure and the rate of pressure change at the brachial artery over time; HR = heart rate; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; PP = pulse pressure; SBP = systolic blood pressure; SV = systemic vascular.

Table 2
Basic characteristics for >80% attendance (adherent group) and ≤80% (non-adherent group).

Baseline characteristic	Adherent group $n = 33$	Non-adherent group $n = 34$	p^*
Average attendance rate (%)	91.0	61.2	< 0.01
Female (%)	21 (64)	25 (74)	0.38
Age, years	64.3 (8.1)	62.3 (8.9)	0.35
Height, m	1.59 (0.08)	1.61 (0.06)	0.34
Weight, kg	59.3 (10.0)	60.3 (10.3)	0.70
BMI, kg/m^2	23.3 (2.9)	23.2 (3.1)	0.90
SBP, mmHg	139 (22.2)	134 (18.4)	0.31
DBP, mmHg	77.8 (10.6)	74.0 (9.6)	0.13
PP, mmHg	60.8 (16.5)	59.5 (14.6)	0.73
HR, beats/min	71.9 (10.7)	72.4 (9.6)	0.85
Laboratory tests			
Fasting sugar, mg/dL	99.1 (6.95)	94.8 (7.66)	0.09
Cholesterol, mg/dL	192 (30.9)	199 (29.1)	0.38
Triglyceride, mg/dL	111 (47.6)	95 (36.4)	0.13
LDL-C, mg/dL	121 (29.6)	128 (28.2)	0.40
Uric acid	5.43 (1.09)	5.34 (1.46)	0.78
hs-CRP	0.16 (0.26)	0.15 (0.15)	0.96
Cardiovascular parameters			
LV dP/dt max, mmHg/sec	1241 (305)	1244 (315)	0.96
LV contractility, 1/sec	14.6 (1.7)	15.2 (2.2)	0.21
Cardiac output, L/min	4.48 (0.96)	4.68 (1.10)	0.44
Cardiac index, L/min/m^2	2.79 (0.52)	2.86 (0.55)	0.58
Stroke volume, mL	63.4 (9.7)	61.4 (8.2)	0.35
Stroke volume index, mL/m^2	38.3 (3.88)	38.9 (3.92)	0.54
SV compliance, mL/mmHg	1.07 (0.26)	1.10 (0.18)	0.55
SV resistance, dynes/sec/cm^5	2784 (326)	1651 (306)	0.09
BA compliance, mL/mmHg	0.058 (0.02)	0.054 (0.02)	0.38
BA distensibility, %/mmHg	5.59 (1.41)	5.62 (1.61)	0.94
BA resistance, dynes/sec/cm^5	287 (154)	281 (92)	0.83

Values are mean (standard deviation) unless otherwise noted.
$^*p$ values that compared adherent and non-adherent group subjects were calculated with two-sample t tests in the case of continuous variables and χ^2 test for nominal variable; BA = brachial artery; BMI = body mass index; DBP = diastolic blood pressure; dP/dt max = isolated pressure and the rate of pressure change at the brachial artery over time; HR = heart rate; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; PP = pulse pressure; SBP = systolic blood pressure; SV = systemic vascular.

4. Discussion

In the present study, we recruited a set of aged subjects from the general population to assess the changes in the Framingham

Table 3
Cardiovascular function changes after 5 months Tai-Chi Chuan exercise between >80% attendance (adherent group) and ≤80% (non-adherent group).

Biomarkers	Adherent group, $n = 33$		Non-adherent group, $n = 34$		p^{**}
	Δ^a	p^*	Δ^a	p^*	
Fasting sugar, mg/dL	−4.50 (6.11)	0.01	−3.89 (5.50)	0.01	0.75
Cholesterol, mg/dL	3.61 (26.6)	0.44	−0.09 (24.2)	0.98	0.55
Triglyceride, mg/dL	−3.12 (42.2)	0.67	18.8 (39.7)	0.01	0.03
LDL-C, mg/dL	2.67 (26.7)	0.56	−1.77 (27.5)	0.71	0.51
Uric acid	0.26 (0.91)	0.11	−0.03 (0.61)	0.75	0.13
hs-CRP	−0.06 (0.26)	0.17	0.03 (0.22)	0.39	0.11
Cardiovascular parameters					
LV ejection time, sec	−0.007(0.04)	0.27	0.002 (0.03)	0.61	0.23
LV dP/dt max, mmHg/sec	47 (255)	0.30	−114 (168)	< 0.01	< 0.01
LV contractility, 1/sec	1.53 (1.93)	< 0.01	−0.33(1.71)	0.27	< 0.01
Cardiac output, L/min	0.46 (0.80)	< 0.01	−0.04 (0.67)	0.70	0.01
Cardiac index, L/min/m^2	0.32 (0.48)	< 0.01	−0.01 (0.39)	0.84	< 0.01
Stroke volume, mL	3.72 (5.4)	< 0.01	−1.26 (5.2)	0.17	< 0.01
Stroke volume index, mL/m^2	2.56 (3.2)	< 0.01	−0.54 (3.0)	0.29	< 0.01
SV compliance, mL/mmHg	0.01 (0.20)	0.70	0.07 (0.22)	0.05	0.23
SV resistance, dynes/sec/cm^5	−303 (332)	< 0.01	−79 (319)	0.16	0.01
BA compliance, mL/mmHg	−0.006(0.01)	0.01	0.001(0.01)	0.55	0.02
BA distensibility, %/mmHg	−0.24 (1.29)	0.29	0.44 (1.53)	0.10	0.05
BA resistance, dynes/sec/cm5	7.67 (68)	0.52	-8.09(76)	0.54	0.37

Values are mean (standard deviation) unless otherwise noted.
$^*p$ values that compared pre and post-test results were calculated with paired-sample t tests; $^{**}p$ values that compared adherent and non-adherent groups were calculated with two-sample t tests; ^{a}denotes the change in parameter in the observation period.
BA = brachial artery; dP/dt max = isolated pressure and the rate of pressure change at the brachial artery over time; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; SV = systemic vascular.

cardiovascular risk biomarkers and cardiac performance parameters before and after TCC intervention. We also evaluated the differences in the above variables between adherent and non-adherent groups of TCC practitioners. We demonstrated for the first time that a 5-month TCC program improved blood sugar control and enhanced cardiac performance parameters in a general aged population. Moreover, we found via noninvasive measurements that participants in ≥80% of sessions of a 5-month TCC program enjoyed better peripheral vascular resistance and cardiac output.

There are several reasons to recommend TCC as an alternative exercise program for patients with or without CVD. First, the effect of TCC on health outcomes in patients with chronic diseases has been extensively reviewed over the years[3,21]. It is effective in treating patients with hypertension, and this effect is greater for SBP versus DBP, which is dependent upon elasticity in the arterial walls[22,23]. Second, TCC has been shown to increase acutely heart rate variability in both young and elderly healthy male subjects. Decreased heart rate variability has been used as a predictor of sudden cardiac death in a variety of disease states, including heart failure[24,25]. Third, regular practice of TCC is associated with enhanced endothelium-dependent dilatation in the skin vasculature of older individuals[26]. The vascular endothelium modulates vascular tone by synthesizing and metabolizing vasoactive substances, and its function is associated with variable CVD[27]. Fourth, and particularly important for crowded cities, TCC does not require special facilities or expensive equipment, and it can be practiced at anytime and anywhere. TCC is also a low-cost, low-technology exercise, and can be easily implemented in a community.

Lee et al have searched and reviewed the evidence for the effects of TCC on CVD. Most studies have evaluated patients with older age, hypertension, diabetes or previous myocardial infarction and the improvements of BP or serum biomarkers after TCC training. The results have revealed that there is encouraging evidence for hypertension therapy, suggesting the potential effectiveness of TCC[14]. However, to the best of our knowledge, there has been no study about the effect of TCC upon cardiac performance either in diseased or normal populations. The reason may be because estimating cardiac output or peripheral vascular resistance using an invasive method is not feasible. Although TCC has been documented to benefit patients who have cardiac disease, who are older, or who tolerate other comorbidity, most practitioners of the exercise are from a general population. Whether TCC is effective for a healthy population has never been previously evaluated. Our current study, therefore, investigated and documented whether TCC is indeed also of benefit for a general healthy population.

In our current study, we recorded the readings of each subject's vascular parameters related to structural properties using a portable, noninvasive, automated monitoring and recording system (DynaPulse). The DynaPulse system can measure a subject's arterial pulsation signals, through a noninvasive cuff device. The pulse dynamic (PD) technique was used to determine SBP, DBP and mean arterial pressure by pulse wave analysis of the oscillometric cuff signal from the brachial artery. The pulse wave analysis PD cardiac output is then derived by further analyzing the changes in PD pressure waveform, which shows good correlation with those of Doppler through a range of dobutamine-stimulated levels[28]. In our study, we demonstrated significantly improved cardiac parameters and SVR in the adherent group, but the BA compliance deteriorated significantly. The reasons remain speculative. On the one hand, in a recent study, Westhoff et al have evaluated the cardiovascular effects of upper-limb aerobic exercise and found that regular arm aerobic exercise, which is similar to TCC, did not lead to an improvement in BA compliance[29]. The authors explained that the workload of arm exercise was too low to lead to a relevant induction of nitric oxide production. On the other hand, the size of the study population might have been too small to create some bias in the measurements of peripheral vascular parameters. Whether TCC has a worse effect on peripheral vascular compliance needs further investigation with prospective randomized studies with larger samples.

There is some possible speculation in our current findings that TCC can improve cardiac performance. First, endothelial dysfunction produced by adipokines is recognized as a key element for various CVDs in patients with poor sugar control[30]. These cytokines could induce endothelial cells to generate excessive reactive oxygen species. The products of the oxidation, in turn, could bind to specific receptors on the endothelial cells, activate transcription of cytokines and chemokines, leading to vascular endothelial cell damage, and initiate the development of atherosclerosis and the deterioration of SVR. TCC has previously been reported to be beneficial for sugar control, which may then lead to improvements in vascular resistance, and hence improved cardiac output. In addition, TCC training has been associated with psychological responses. Several studies have demonstrated that the regular practice of TCC could reduce psychological stress, such as tension, anxiety and depression, which may serve as factors to deteriorate cardiac performance[31]. Moreover, despite the slow motion of TCC, it is considered to be a moderately intense form of aerobic exercise[5]. Exercise training has been considered the major, most important component of cardiac rehabilitation, and is characterized by improvement in LV function[32].

We recognize the limitations of this study. First, the subjects were recruited from a health promotion at TCC clubs, so they may have been more inclined to engage in other self-care activities than the typical general population. Second, those who attended $<$80% of the TCC program for $>$5 months may have had other reasons for not performing the self-care activities, or they may have suffered a lower quality of life as a result, in ways that were not captured in the present study. Third, our current study was limited by the small number of study subjects and the indirect methods for measuring cardiac performance. Fourth, some confounding factors such as smoking habit, activities of daily life, and menu of daily diets besides TCC were not addressed and controlled in the analysis.

TCC is a well-tolerated exercise for the aged population. Metabolic syndrome and cardiac performance are important predictors for morbidity and mortality in this subgroup population. In conclusion, a Yang-style TCC program was effective in reducing blood glucose and other cardiovascular risk biomarkers, as well as most of the cardiac performance parameters, including cardiac output, stroke volume and vascular compliance, after TCC was practiced regularly over 5 months in an aged population. Whether the benefits of TCC come from the exercise or the relaxation component needs further investigation. The clinical implications of the changes in vascular compliance found in the present study and others suggest that TCC may reduce the complications and mortality associated with hypertension and atherosclerosis. However, longitudinal studies over several years are required to determine the effects of TCC on these clinically important outcomes.

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