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Physical activity and progression of carotid intima-media thickness in patients with coronary heart disease

Shinji Sato (MD)^{a,*}, Shigeru Makita (MD)^a, Ryusei Uchida (MD)^a,
Shunich Ishihara (MD)^b, Mitsuru Majima (MD)^a

^a Department of Rehabilitation Medicine, International Medical Center, Saitama Medical University, 1397-1 Yamane, Hidaka-City, Saitama 350-1298, Japan

^b Department of Human Sciences, Bukyo University, Saitama, Japan

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KEYWORDS

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Summary

Objective: We conducted the present study to determine the level of physical activity required to retard the progression of carotid intima-media thickness (IMT) in patients with coronary heart disease (CHD).

Patients and main outcome measurements: The daily walking distance (km/day) of 40 patients with CHD (male/female ratio: 37/3, mean age: 61.2 years, mean interval time after a coronary event 16.2 months) was examined. Carotid IMT examinations (B-mode ultrasonography) were performed at the baseline and after 6 months.

Results: Among the patients, the average walking distance was 4.00 km/day. Walking distance was inversely associated with IMT progression ($r = -0.51$, $p < 0.01$). Multivariate logistic regression analysis revealed that walking distance ($p = 0.024$) is a predictor for IMT progression independent of classical cardiovascular risk factors. Receiver operating characteristic analysis showed that the walking distance of 4.25 km was strongly predictive of IMT preservation (sensitivity 64.0%, specificity 73.3%) in CHD patients.

Conclusions: Our data suggested that an increase in the daily walking distance could retard the progression of carotid IMT in patients with CHD. Cardiology medical staff should encourage their patients to expend an average of 4–5 km in daily walking distance for the secondary prevention of cardiovascular disease.

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Introduction

Measurements of carotid intima-media thickness (IMT) have been used previously for the noninvasive

* Corresponding author. Tel.: +81 42 984 4367;
fax: +81 49 294 2267.
E-mail address: shinjisato2005hawaii@yahoo.co.jp (S. Sato).

detection of carotid atherosclerosis lesions. A thickened IMT is correlated empirically with the risk of future cardiovascular events, such as myocardial infarction and stroke [1]. Furthermore, a previous autopsy study has identified a relationship of thickened IMT with the grade of lesion severity in the carotid and other arteries [2]. These interrelations suggest that IMT may serve as a surrogate variable when studying general atherosclerosis.

It is generally accepted that physical activity and exercise training have an antiatherogenic effect [3] that may be related to a reduction in the progression of IMT. Only a few studies have been conducted on the effect of increased physical activity on IMT. A diet-and-exercise intervention slowed menopause-related IMT progression [4]. Physically sedentary hypertensive patients were shown to have significantly greater levels of IMT than active hypertensive patients [5]. To our knowledge, there are no guidelines on the physical activity level necessary to retard IMT progression. We conducted the present study to determine the level of physical activity required to retard IMT progression in patients with coronary heart disease (CHD).

Methods

Patients

The study population consisted of 40 eligible patients with stable CHD, aged 45–79 years (mean age: 61.2 ± 7.13 years), who were admitted to the Department of Rehabilitation Medicine in Saitama Medical University Hospital between September 2004 and April 2005. These patients visited our hospital for a health counseling and an exercise prescription. Of these patients, 23 had undergone percutaneous transluminal coronary angiography (PTCA) previously and the other 17 had undergone coronary artery bypass grafting (CABG); the mean interval time after the coronary event was 16.2 ± 12.3 months. Inclusion criteria were who had carotid plaque, defined as focal IMT > 1.1 mm in the CCA and bifurcation, but no symptoms of carotid artery disease. Exclusion criteria included uncontrolled heart failure, severe or unstable angina pectoris, and uncontrolled hypertension, hyperlipidemia or diabetes mellitus. To reduce the confounding effects of disease on the capacity to walk, patients with stroke and intermittent claudication were excluded. Patients, who were not able to appear for check-up visits, and patients refusing to give their written consent, were also excluded.

Baseline examination

At the baseline, all patients underwent a full physical examination to obtain the body mass index (BMI), systolic blood pressure (SBP), and peak oxygen uptake, which were measured by cardiac pulmonary exercise testing (CPX). CPX was performed in the upright position on a bicycle ergometer (Strength Ergo 8, Fukuda Denshi, Tokyo, Japan) with an initial workload of 0 Watt (W), with subsequent increments of 15 W every minute until exhaustion. Expired gas exchange during symptom-limited exercise testing was measured by breath-by-breath analysis with a metabolic cart (AE300s, MINATO, Tokyo, Japan). From these measurements, oxygen uptake was calculated every 10 s.

For the assessment of physical activity, information on the amount of daily walking distance was collected by a trained interviewer [6]. All patients were asked about the average distance they walked per day. Additional characteristics included age, gender, and history of hypertension (defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg or antihypertensive treatment), diabetes (defined with the Japan diabetes society criteria published in 1999 [7]), and hyperlipidemia (defined as blood triglycerides > 150 mg/dl or blood total cholesterol levels > 220 mg/dl or treatment with statins).

Carotid ultrasound

Carotid ultrasound examinations were performed at the baseline and after 6 months. Details of data collection and evaluation methods for IMT of the common carotid artery have been published elsewhere [8,9]. In brief, one trained technician with no knowledge of the treatment assignment performed all the examinations. Ultrasonography was performed with the patients in the supine position, using a CF-sonic UF7500 (Fukuda-Denshi, Tokyo, Japan) with a 7.5 MHz transducer. The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo. Measurements of carotid IMT were performed on the far walls of the common carotid artery (CCA). IMT was calculated as the average value of the IMT measurements for six sites (three on each side) in the CCA. The examinations were video-graphic printed with a micro-caliper for subsequent analyses. To evaluate the validity of the ultrasonographic method, we performed repeated scans of the same patients 6 times within 1 month. The average difference in IMT among these measurements was 2.43% of the mean IMT. The change

Table 1 Demographic and clinical characteristics for changes in relative IMT after 6 months of study

	All patients (n=40)	Progression of IMT (n=15, 37.5%)	No progression of IMT (n=25, 62.5%)	p
IMT at baseline (mm)	0.92 ± 0.18	0.95 ± 0.19	0.90 ± 0.17	0.73
ΔIMT (mm)	0.01 ± 0.05	0.057 ± 0.04	-0.018 ± 0.03	<0.01
Distance walked (km/day)	4.00 ± 1.8	3.18 ± 1.7	4.49 ± 1.7	0.03
Cardiovascular risk factors				
Age (year)	61.2 ± 7.1	59.2 ± 9.5	59.2 ± 5.8	0.19
Gender (n) female (%)	3 (7.5)	1 (6.7)	2 (8)	0.88
BMI (kg/m ²)	24.3 ± 2.0	24.4 ± 1.5	24.3 ± 2.3	0.87
SBP (mmHg)	127.3 ± 19.7	136.7 ± 17.6	121.6 ± 19.0	0.02
Peak VO ₂ (ml/(min kg))	20.5 ± 4.3	20.4 ± 4.5	20.5 ± 4.3	0.98
Hypertension (n) (%)	30 (75)	12 (80)	18 (72)	0.57
Diabetes (n) (%)	19 (47.5)	9 (47.4)	10 (52.6)	0.22
Hyperlipidemia (n) (%)	25 (62.5)	7 (46.7)	18 (72)	0.11
Medications				
ACE inhibitors (n) (%)	21 (52.5)	10 (66.7)	11 (44)	0.17
β-Blockers (n) (%)	30 (74)	12 (80)	18 (72)	0.57
Calcium-channel blockers (n) (%)	2 (5)	1 (6.7)	1 (4)	0.71
Aspirin (n) (%)	35 (87.5)	14 (93.3)	21 (84)	0.39
Statis user (n) (%)	18 (40)	5 (33.3)	13 (52)	0.25

in IMT ($\Delta\text{IMT} = \text{IMT after 6 months} - \text{IMT at baseline}$) within 6 months was used as an index of IMT progression. Furthermore, we dichotomized responses into “patients with progression ($\Delta\text{IMT} > 0 \text{ mm}$)” or “without progression ($\Delta\text{IMT} \leq 0 \text{ mm}$)”.

Statistical analysis

All values were expressed as the mean \pm standard deviation. Difference between groups were assessed by using the *t*-test or χ^2 test as appropriate. Correlations between the ranges of IMT changes and daily walking distance were evaluated by calculating Pearson's correlation coefficients. Forward multiple logistic regression analysis was performed to detect independent risk factors for the progression of IMT. Receiver operating characteristic (ROC) analysis was constructed for variables retained in the multivariate Cox regression analysis. Optimal cut-off values (highest combination of sensitivity/specificity) of daily walking distance were identified for the course of IMT progression via ROC analysis. A value of $p < 0.05$ was regarded as significant.

Results

All of the 40 enrolled patients fully completed the study. During the study period, medical treatment and physical activity was maintained almost constant, and no episodes of severe clinical events were recorded. The basic clinical characteristics are given in Table 1.

At the baseline, the average walking distance was $4.00 \pm 1.8 \text{ km/day}$. Walking distance was inversely associated with the ΔIMT as a marker of disease progression ($r = -0.51$, $p < 0.01$; Fig. 1). The patients were divided in two groups retrospectively: patients with progression ($n = 15$, mean $\Delta\text{IMT} = 0.057 \pm 0.04 \text{ mm}$) and those without progression ($n = 25$, mean $\Delta\text{IMT} = -0.018 \pm 0.03 \text{ mm}$). Patients with progression had a significant lower walking distance (3.18 ± 1.7 vs. $4.49 \pm 1.7 \text{ km}$; $p = 0.03$) and higher SBP (136.7 ± 17.6 vs. $121.6 \pm 19.0 \text{ mmHg}$; $p = 0.02$) than patients without progression (Table 1).

To identify possible mechanisms for the observed changes in IMT, baseline characteristics, including cardiovascular risk factors, medications and walking distance, were analyzed in terms of their relation to the IMT progression. The best multiple linear regressions model for predicting the IMT progression included the walking distance ($p = 0.024$) and resting SBP ($p = 0.030$).

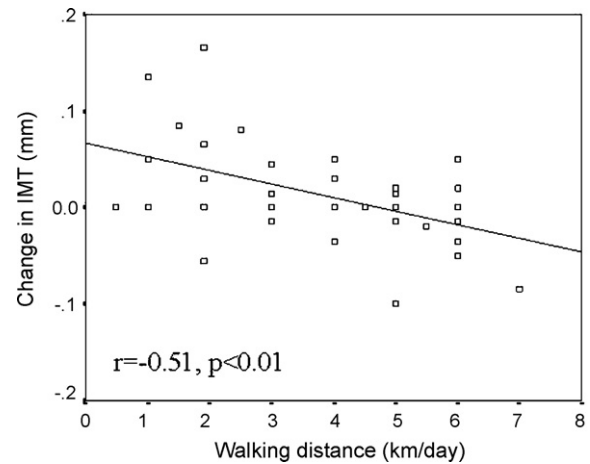


Figure 1 Correlation of walking distance and change in intima-media thickness (IMT).

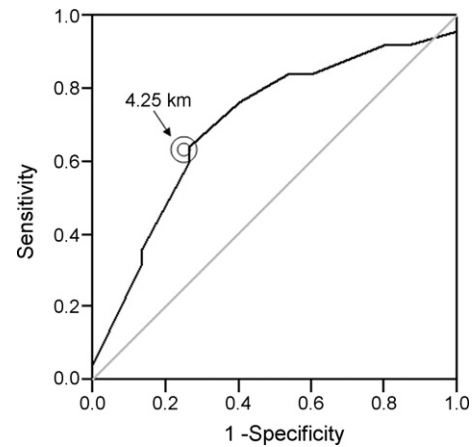


Figure 2 Receiver–operator characteristic curved for detection of IMT preservation by measures of walking distance.

ROC analysis showed that the walking distance of 4.25 km was strongly predictive of IMT preservation (sensitivity 64.0%, specificity 73.3%) (Fig. 2).

Discussion

The findings of this study indicated that enhanced physical activity is negatively correlated with the progression of carotid atherosclerosis lesions evaluated as mean IMT in patients with stable CHD. This result further supports the importance of physical activity for improving general atherogenesis in CHD patients. Additionally, our data suggested that patients who walked more than 4.25 km/day had significantly reduced progression of carotid IMT. Hambrecht et al. showed that even in patients with CHD who walked the equivalent to at least 1533 kcal/week, the beneficial effect of walking

on coronary atherosclerosis lesions persisted [10]. On average, 1533 kcal/week must be expended, amounting to 4–5 km/day of walking distance. The combined results of the present and previous studies suggest that the amount of 4–5 km/day of walking distance in leisure time physical activity is necessary to retard the progression of general atherosclerosis in patients with CHD.

There have been very few clinical trials on the association between physical activity and IMT progression. The Women's Healthy Lifestyle Project (WHLPP) trial reported that a diet-and-exercise intervention slowed menopause-associated IMT progression among women who had reached the peri-menopause or post-menopause period [4]. This attempt was made to examine only healthy women. Accordingly, this is the first study showing that a higher activity level results in a markedly reduced IMT progression in patients with CHD.

The mechanism by which high-level physical activity induced favorable changes in IMT remains obscure. Previous trials suggest that the lipid-lowering effect is a key element in carotid atherosclerosis regression. In the regression growth evaluation statin study (REGRESS) [11], the effects of pravastatin treatment on the mean and maximal IMT of men with CHD were highly significant. In other lipid intervention studies, treatment effects were also significant [12–14]. The interventional approach to reducing insulin resistance also could result in the regression of carotid atherosclerosis. A prospective study on pioglitazone therapy in patients with type 2 diabetes resulted in a significant decrease in mean IMT [15]. It is generally accepted that physical activity and exercise training improved the serum lipid profile, insulin resistance and other metabolic disorders. Thus, improvement in several components of the metabolic risk factors jointly may be associated with a markedly reduced IMT progression in the high-level physical activity group.

In the REGRESS trial, relative regression of the mean IMT was 6–7% in 2 years [11]. Riegger et al. demonstrated that 52-week aggressive fluvastatin therapy led to mean IMT regression of 2–3% in patients with CHD [16]. Accordingly, the regression of mean IMT in the high-level physical activity group in our study seemed to be of the same order of magnitude as regression achieved with high-dose statin therapy in patients with CHD. However, we predict that this excellent benefit was achieved not only by the walking, but also through good lipid control and statin use greater than 50% in the high-level physical activity group.

Our study had several limitations. Carotid IMT is now widely accepted as a validated surrogate

marker for carotid atherosclerotic lesions [11,17]. Yet, there is no generally accepted standardized method for measuring IMT. In our examination, only the IMT data of images of the far walls were analyzed. The latter is justified by the better reproducibility of measurements from this site and the difficulties in obtaining measurements from the near walls. Since we were interested mainly in progression/regression of general atherosclerosis, we did not record the maximal IMT and the shape and quality of plaque, but measured the mean IMT at a defined location. It is likely that each of these markers has a different role to play in the evaluation of atherosclerosis [18]. Further studies are needed to investigate the dose-dependent effects of physical activity on the maximal IMT and plaque formation. In addition, we did not obtain relevant clinical data for the atherosclerotic risk factors, such as LDL cholesterol, HDL cholesterol, fasting serum glucose, fasting serum insulin and HbA1c. Therefore, our analysis, which was adjusted for these intermediate risk factors, may have underestimated the effect of physical activity on IMT progression. Another limitation of our study was the self-reported physical activity. Using a self-reported questionnaire to assess lifestyle habits is generally a crude approach. Misclassification might result in an overestimation of the relationship between physical activity and IMT changes in our study.

Nonetheless, our data suggested that an increase in the daily walking distance could retard the progression of carotid atherosclerotic lesions in CHD patients. Cardiology medical staff should encourage their patients to expend an average of 4–5 km in daily walking distance for the secondary prevention of cardiovascular disease.

References

- [1] O'Leary DH, Polak JF, Kronmal RA, Monolio TA, Burke GL, Wolfson SK. Carotid artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *Cardiovasc Health Study Collab Res Group. N Engl J Med* 1999;340:14–22.
- [2] Sorensen KE, Kristensen IB, Celermajer DS. Atherosclerosis in the human brachial artery. *J Am Coll Cardiol* 1997;29:318–22.
- [3] Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease. A statement from the council on clinical cardiology (subcommittee on exercise, rehabilitation, and prevention) and the council on nutrition, physical activity, and metabolism (subcommittee on physical activity). *Circulation* 2003;107:3109–16.

- [4] Wildman RP, Scott LL, Brockwell S, Kuller LH, Sutton-Tyrrell K. A dietary and exercise intervention slows menopause-associated progression of subclinical atherosclerosis as measured by the intima-media thickness of the carotid arteries. *J Am Coll Cardiol* 2004;44:579–85.
- [5] Casiglia E, Palatini P, Da Ros S, Pagliara V, Puato M, Dorigatti F, et al. Effect of blood pressure and physical activity on carotid artery intima-media thickness in stage 1 hypertensives and controls. *Am J Hypertens* 2000;13:1256–62.
- [6] Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. *JAMA* 2004;292:1447–53.
- [7] Kuzuya T. Outline of revision of classification and diagnostic criteria of diabetes mellitus in Japan. *Nippon Rinsho (Jpn J Clin Med)* 1999;57:561–6.
- [8] Honda N, Matsumoto M, Maeda H, Hougaku H, Kamada T. Ischemic stroke evens and carotid atherosclerosis: results of the Osaka follow-up study for ultrasonographic assessment of carotid atherosclerosis (the OSACA study). *Stroke* 1995;26:1781–6.
- [9] Koshiyama H, Shimono D, Kuwamura N, Minamika J, Nakamura Y. Inhibitory effect of pioglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab* 2001;86:3452–6.
- [10] Hambrecht R, Niebauer J, Marburger C, Grunze M, Kalberer B, Hauer K, et al. Various Intensities of leisure time physical activity in patients with coronary artery disease: effects on cardiorespiratory fitness and progression of coronary atherosclerotic lesions. *J Am Coll Cardiol* 1993;22:468–77.
- [11] De Groot E, Jukema JW, Montauban van Swijndregt AD, Zwinderman AH, Ackerstaff RGA, Van Der Steen AFW, et al. B-mode ultrasound assessment of pravastatin treatment effect on carotid and femoral artery walls and its correlations with coronary arteriographic findings: a report of the Regression Growth Evaluation Statin Study (REGRESS). *J Am Coll Cardiol* 1998;31:1561–7.
- [12] Blankenhorn DH, Selzer RH, Crawford DW, Barth JD, Liu CR, Liu CH, et al. Beneficial effects of colestipol therapy on the common carotid artery. *Circulation* 1993;88:20–8.
- [13] Riitta S, Kristiina N, Elina P, Juha R, Rene B, Jorn-Soon P, et al. Kuopio atherosclerosis prevention study (KAPS): a population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation* 1995;92:1758–64.
- [14] Sawyama Y, Shimizu C, Maeda N, Tatsukawa M, Kinukawa N, Koyanagi S, et al. Effects of probucol and pravastatin on common carotid atherosclerosis in patients with asymptomatic hypercholesterolemia. *J Am Coll Cardiol* 2002;39:610–6.
- [15] Langenfeld MR, Forst T, Hohberg C, Kann P, Lubben G, Konrad T, et al. Pioglitazone decreases carotid intima-media thickness independently of glycemic control in patients with type2 diabetes mellitus. Results from a controlled randomized study. *Circulation* 2005;111:2525–31.
- [16] Riegger G, Abletshauser C, Ludwig M, Schwandt P, Widimsky J, Weidinger G, et al. The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment. *Atherosclerosis* 1999;144:263–70.
- [17] Bots ML, Grobbee DE. Intima-media thickness as a surrogate marker for generalized atherosclerosis. *Cardiovasc Drugs Ther* 2002;16:341–51.
- [18] Makita S, Ohira A, Tachieda R, Itoh S, Moriai Y, Niinuma H, et al. Dilatation and reduced distensibility of carotid artery in patients with abdominal aortic aneurysms. *Am Heart J* 2000;140:297–302.

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