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Chinese Adults Are Less Susceptible Than Whites to Age-Related Endothelial Dysfunction

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Objectives. **We sought to assess the effects of aging on the endothelial physiology of a group of Chinese adults.**

Background. **Several studies have documented an association between aging and progressive arterial endothelial dysfunction in white subjects. We hypothesized that age-related endothelial dysfunction, an important event in atherosclerosis, might be less marked in southern Chinese subjects, in whom the prevalence of coronary heart disease is only ~20% of that in industrialized countries.**

Methods. **We studied endothelial function in 76 healthy adults aged 16 to 70 years: 38 Chinese from a village of 3,000 people in southern China and 38 white subjects from Sydney, Australia. In each ethnic group, there were 19 younger persons (16 to 40 years) and 19 older adults (55 to 70 years). None had evidence of diabetes, hypertension or clinical vascular disease or had ever been regular cigarette smokers. With the use of high resolution external vascular ultrasound, brachial artery diameter was measured at rest, after flow increase (causing endothelium-dependent dilation) and after sublingual nitroglycerin (an endothelium-independent dilator).**

Results. **Endothelium-dependent dilation was similar in young Chinese (mean ± SD 8.3 ± 2.5%), young whites (7.9 ± 2.0%) and older Chinese (6.8 ± 2.9%), but it was significantly impaired in older whites (1.8 ± 2.5%, $p < 0.001$ by analysis of variance). On multivariate analysis, older age was associated with impaired endothelium-dependent dilation ($p < 0.001$) (independent of the effects of serum cholesterol, gender and vessel size) in the white but not in the Chinese subjects ($p = 0.83$). Nitroglycerin-induced dilation was not significantly different with aging in either ethnic group.**

Conclusions. **Endothelium-dependent dilation is similar in the arteries of healthy young Chinese and white adults. With older age, however, Chinese subjects are less susceptible to impaired endothelial function.**

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Endothelial dysfunction is an important early event in experimental models of atherosclerosis (1,2). In humans, traditional coronary risk factors have been associated with impairment of endothelium-dependent dilation, both in asymptomatic subjects at risk of atherosclerosis (3–6) and in subjects with established coronary artery disease (7,8). Aging is one of the most important risk factors for symptomatic atherosclerosis (9,10), and several recent studies have uniformly found an association between older age and progressive endothelial dysfunction in symptomatic (6,11) and asymptomatic (12) white subjects.

About one quarter of the world's population (1.2 billion people) live in China; however, no studies have yet assessed endothelial function in mainland Chinese subjects with or without risk factors for atherosclerosis. Because the risk of coronary artery disease is much lower in southern Chinese than in white subjects in westernized countries (13), we hypothesized that Chinese subjects might be less susceptible to age-related endothelial dysfunction. To study the effects of aging as such, we investigated arterial endothelial physiology in groups of younger and older adults with no known risk factors for atherosclerosis, other than aging, in a village in southern China and in whites from a typical industrialized city in Australia.

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Methods

Subjects. We studied 76 subjects aged 16 to 70 years of age; none had diabetes or any history of hyperlipidemia, hypertension or a family history of premature vascular disease. None had regularly smoked cigarettes or had been exposed to environmental tobacco smoke. All were clinically well and taking no regular cardiovascular medications. None of the postmenopausal women studied had ever taken hormone replacement therapy. An accurate assessment of menstrual phase was not obtained from the premenopausal women. Subjects were recruited from community volunteers, and all gave informed consent in their native language. The study was approved by our institutional committees on ethical practice.

The Chinese subjects were studied in Shek Kei Village, on the outskirts of Pan Yu, in Guangdong province, southern China. The population of this village is ~3,000, although people from this village are not geographically isolated, and intermarriage with adults in Pan Yu is common. Adults in Shek Kei village are similar in body size, lifestyle (including diet, exercise and smoking habits), personal income and disease patterns to the other inhabitants of Guangdong province. Most of the villagers still consume a traditional Chinese diet, based on vegetables, rice, fish and green tea. The annual rate of acute myocardial infarction in this region of China is ~35/100,000 persons (13). The white subjects were studied in Sydney, Australia, where the population is ~3.8 million and the annual rate of acute myocardial infarction is ~175/100,000 (14).

Over a 2-week period, we performed studies on 142 Chinese community volunteers in Shek Kei Village. On the basis of our previous study on the relation between aging and endothelial function in white subjects (12), in which we documented an age-related decline in endothelium-dependent dilation that occurs between 40 and 55 years of age, we prospectively defined two age groups for inclusion in this study. "Older" adults were defined as those aged 55 to 70 years and "younger" adults as those aged 16 to 40 years. As in our previous study (12), we also decided prospectively to study subjects in these age groups who were free of known vascular risk factors (such as smoking and diabetes mellitus) in order to assess the arterial effects of aging as such. Of the Chinese adults studied, 19 older subjects (6 men, 13 women) fulfilled the prospectively defined criteria for age and absence of known cardiovascular disease or risk factors. We compared these subjects with the first 6 male and 13 female Chinese subjects studied whose age was in the prospectively defined younger age range. These groups were then compared with age- and gender-matched subjects whom we had studied either recently or after our studies in China and Sydney, Australia. Therefore in each ethnic group, there were 19 subjects aged 16 to 40 years (younger adults) and 19 subjects aged 55 to 70 years (older adults).

To minimize any selection bias resulting from the use of community volunteers, we applied similar strategies for recruitment in China and Australia. Posters advertising the study projects were placed in the community in the vicinity of the hospital or health center. Respondents were screened for the predefined age and risk factor criteria as outlined, and they underwent study if they were suitable. All advertising material was written only in the local language in each center.

Study design. Each subject made one visit to the study hospital or health center during which a medical history was taken, height and weight were recorded, supine rest blood pressure was measured and vascular reactivity of the brachial artery was analyzed. Body mass index was calculated as weight (kg) divided by height (m^2). In every case, venous blood was sampled after a 14-h fast for analysis of lipid levels, on the same day or within 1 week of the arterial studies. All scans in both study locations were performed by the same operators.

Fasting serum cholesterol and triglycerides were assayed enzymatically by using the Boehringer Mannheim Hitachi 747 (Sydney laboratory) or 911 (Hong Kong laboratory) analyzer. High density lipoprotein cholesterol was measured after precipitation with phosphotungstate-magnesium. Low density lipoprotein cholesterol was calculated by means of the Friedewald formula (15). Both laboratories performing the lipid analyses are currently accredited with intraassay imprecision of their cholesterol measurement <3% and accuracy standardized by the Center for Disease Control–National Heart, Lung, and Blood Institute (U.S.) program (for example, the absolute bias from the Abell-Kendall method was −0.1 mmol/liter at 5.2 and 6.2 mmol/liter, at the time of this study).

The ultrasound method for measuring endothelium-dependent and endothelium-independent arterial dilation has been described in detail previously (3–5). The diameter of the brachial artery was measured on B-mode ultrasound images, using a 7.0-MHz linear-array transducer and a standard Acuson 128 XP/10 system (Mountain View). In all studies, longitudinal scans of the artery were obtained at rest, then during reactive hyperemia produced by inflation of a pneumatic tourniquet placed on the forearm to 250 mm Hg for 4.5 min, followed by release (with increased flow producing endothelium-dependent dilation) and finally after sublingual nitroglycerin (an endothelium-independent dilator). Doppler-derived arterial flow was measured at rest and during hyperemia (3).

Data analysis. In every case, the diameter of the artery was measured by two independent observers who did not know the identity of the subjects or the stage of the experiment. Endothelium-dependent and nitroglycerin-induced dilation (expressed as percent change in vessel diameter) were calculated from each observer's measurements, as previously described (3–5), and the average results of the two observers were recorded. The same group of observers analyzed scans from both participating centers. We (16) recently documented the accuracy, reproducibility and low interobserver error for these measurements of arterial physiology. Reactive hyperemia was calculated as the maximal flow recorded in the 1st 15 s after cuff deflation divided by rest flow, as previously described (3–5).

Statistical analysis. Descriptive data are expressed as mean value ± SD, unless otherwise stated. Baseline characteristics of the young Chinese were compared with those of the

Table 1. Baseline Characteristics of the Chinese and White Subjects

	Younger Chinese (n = 19)	Younger Whites (n = 19)	Older Chinese (n = 19)	Older Whites (n = 19)	p Value*
Age (yr)	29 ± 5	28 ± 6	63 ± 5	63 ± 4	< 0.001†
Range	16–40	16–40	55–70	55–70	
Gender (% female)	68%	68%	68%	68%	1.0
Body mass (kg)	56.1 ± 7.9	66.5 ± 6.8	57.3 ± 11.7	69.8 ± 9.1	< 0.001‡
Height (cm)	156 ± 16	171 ± 4	159 ± 9	168 ± 8	0.002‡
Body mass index	23.9 ± 7.9	22.8 ± 2.7	22.6 ± 3.8	24.9 ± 3.4	0.45
SBP (mm Hg)	115 ± 11	108 ± 9	129 ± 14	127 ± 13	< 0.001†
DBP (mm Hg)	76 ± 10	75 ± 7	83 ± 8	79 ± 11	0.10
Cholesterol (mmol/liter)					
Total	4.9 ± 1.0	4.6 ± 0.8	5.7 ± 1.2	5.8 ± 0.9	0.002†
LDL	3.1 ± 1.4	2.7 ± 1.0	3.4 ± 0.9	3.4 ± 0.8	0.31
HDL	1.3 ± 0.3	1.5 ± 0.3	1.4 ± 0.5	1.5 ± 0.4	0.38
Triglycerides (mmol/liter)	0.9 ± 0.4	0.9 ± 0.4	1.4 ± 1.0	1.4 ± 0.9	0.09
Vessel size (mm)	3.5 ± 0.5	3.4 ± 0.6	3.6 ± 0.6	3.7 ± 0.5	0.27
Baseline flow (ml/min)	58 ± 36	72 ± 44	64 ± 46	76 ± 40	0.16

*Analysis of variance for detection of differences among the four groups. †By pairwise comparison, ages and total cholesterol and systolic blood pressure levels were similar in the two groups of younger and the two groups of older adults but significantly higher in the older than in the younger Chinese and whites ($p < 0.01$). ‡Body mass index and height were greater in both groups of whites than in both groups of Chinese subjects ($p < 0.01$) but were similar in younger and older subjects of the same ethnic group ($p > 0.20$). Unless otherwise indicated, data are presented as mean value ± SD. DBP = diastolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; SBP = systolic blood pressure.

young whites by independent samples *t* tests; similar comparisons were performed for the older subjects. Analysis of variance for the four groups (young and old Chinese, young and old whites) was performed, based on a 2 × 2 factorial design, followed by the Student-Newman-Keuls test for multiple comparisons. There was no significant interaction between age and ethnic group when an interaction factor for these two variables was entered into the analysis of variance model for endothelium-dependent dilation, which was the study's primary end point. In the Chinese and white subjects, the determinants of endothelium-dependent dilation and nitroglycerin-induced dilation were assessed by multiple linear regression analysis, with age group (younger or older), ethnic group (Chinese or white), gender, blood pressure, total or low density lipoprotein cholesterol, degree of hyperemia and vessel size entered as independent variables. Statistical significance was inferred at a two-tailed p value of < 0.05.

Results

Baseline characteristics (Table 1). The younger adult subjects had an average age of 28 ± 4 years (range 16 to 40), with similar ages in the Chinese and white groups. For the older adult subjects, the average age was 63 ± 4 years (range 55 to 70), with similar ages in the two ethnic groups. There were 6 male and 13 female subjects in each of the younger and older groups. The older Chinese women were studied 11 ± 6 years and the older Caucasian women 11 ± 3 years ($p = 0.75$) after their last menstrual period. Other important baseline characteristics, such as serum cholesterol levels, vessel size, baseline flow and blood pressure, were also similar in the different ethnic groups (Table 1), although blood pressure and cholesterol levels were higher in the older than in the younger subjects (both Chinese and white). Body mass and height were greater in both groups of white than in Chinese subjects, but they were similar in the younger and older subjects of the same ethnic group. Body mass index was similar in all four groups.

Vascular study results (Table 2). The average degree of reactive hyperemia after cuff release was >400% for all four groups studied, but it was higher in the Chinese than in the white subjects. In response to this increase in flow, arterial dilation was 8.3 ± 2.5% (range −0.3% to 15.3%) in the younger Chinese, 7.9 ± 2.0% (range 2.1% to 12.7%) in the younger whites, 6.8 ± 2.9% (range 0.1% to 11.3%) in the older

Table 2. Vascular Study Results for the Chinese and White Subjects

	Younger Chinese (n = 19)	Younger Whites (n = 19)	Older Chinese (n = 19)	Older Whites (n = 19)	p Value*
EDD (%)	8.3 ± 2.5	7.9 ± 2	6.8 ± 2.9	1.8 ± 2.5	< 0.001†
NTG (%)	18.8 ± 5.4	19.8 ± 4	17.1 ± 6.1	15.7 ± 5.3	0.10
Hyper (%)	688 ± 216	459 ± 210	729 ± 420	501 ± 225	0.008‡

*Analysis of variance for detection of differences between groups. †By pairwise comparison, endothelium-dependent dilation was similar in all groups except the older whites, in whom it was significantly lower ($p < 0.001$). ‡By pairwise comparison, hyperemia was lower in both groups of whites than in both groups of Chinese subjects ($p < 0.01$). EDD = endothelium-dependent dilation; Hyper = reactive hyperemia; NTG = nitroglycerin-induced dilation.

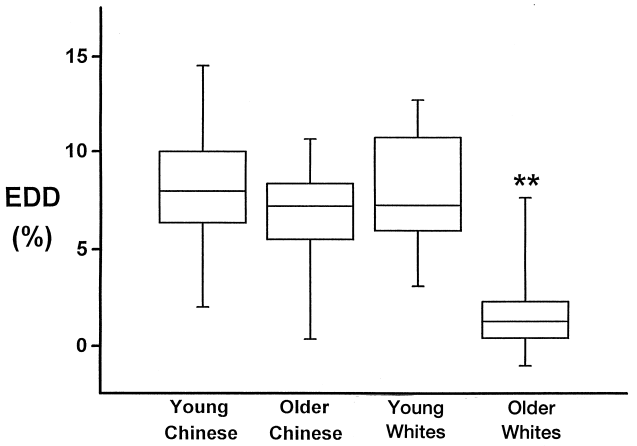

Figure 1. Comparison of endothelium-dependent dilation (EDD) in four groups of healthy adults (median values with bars indicating standard errors). By analysis of variance followed by pairwise comparisons, endothelium-dependent dilation was significantly lower in the older whites than in the three other groups, whose values did not differ significantly from each other. In this box plot, each **box** represents the interquartile range, the **line within each box** represents the median value, and the **error bars** encompass 95% of values, for each group of subjects. **$p < 0.001$.

Chinese (the latter three groups were not different by analysis of variance), but it was significantly lower in the older whites ($1.8 \pm 2.5\%$, range -1.1% to 9.7%, $p < 0.001$) (Fig. 1). Similar results by analysis of variance and pairwise testing were obtained when men and women from the study were analyzed separately. By contrast, nitroglycerin-induced responses were similar in all four groups studied ($p = 0.10$).

When only the 38 white subjects were considered, older age group was the most significant predictor of impaired endothelium-dependent dilation (partial $r = -0.95$, $p < 0.001$), independent of the effects of cholesterol, blood pressure, gender, degree of hyperemia and vessel size (Table 3). Similar results were obtained if age in years rather than age group (older or younger) was entered into the multivariate model ($r = -0.67$, $p < 0.001$). In the 38 Chinese subjects, older age group was not significantly associated with endothelium-dependent dilation (partial $r = -0.03$, $p = 0.83$), nor was cholesterol or blood pressure levels, degree of hyperemia or vessel size. These results were similar when white or Chinese men and women were analyzed separately. In the 38 younger subjects, ethnic group was not related to endothelium-dependent dilation ($p = 0.84$), nor was cholesterol, blood pressure, vessel size or degree of reactive hyperemia ($p > 0.10$ for all). However, in the 38 older subjects, white race was significantly associated with impaired endothelium-dependent dilation ($p < 0.001$), independent of the other variables measured. When similar multivariate analyses were performed with nitroglycerin response as the dependent variable, only vessel size was significantly (inversely) correlated in each subgroup studied ($p \leq 0.02$). Specifically, age was not related to nitroglycerin response in either the white or the Chinese subjects.

Discussion

This study has shown that older Chinese adults, living in southern China, are less susceptible to the age-related impairment of endothelial function that is seen in healthy white adults. These data suggest that progressive endothelial dysfunction is not an inevitable consequence of aging but might be related to prolonged exposure to environmental factors more prevalent in westernized countries than in China. Because we studied relatively small numbers of older subjects, and no adults >70 years of age, it is possible that there is an age-related decline in arterial reactivity in old Chinese adults; however, any such decline appears to be much less marked than in white adults.

Endothelial function and the effects of aging. Endothelial dysfunction is an important event, both in early atherogenesis (3–7) and in advanced atherosclerosis, where endothelial responses may influence dynamic plaque behavior (17–19). Therefore, the relative preservation of endothelial function in older Chinese may be an important contributing factor to the low prevalence of clinical coronary disease observed in China to date, despite the high prevalence of cigarette smoking in Chinese men (20) and the surprisingly high cholesterol levels observed in this study (comparable to those in the Caucasian subjects).

Aging has been associated with several cardiovascular

Table 3. Multivariate Analysis for the Determinants of Endothelium-Dependent Dilation in the White and Chinese Subjects

	White Subjects (n = 38)		Chinese Subjects (n = 38)	
	Partial r Value	p Value	Partial r Value	p Value
Age	−0.95	< 0.001	−0.03	0.88
SBP	0.17	0.17	−0.37	0.07
Gender	0.24	0.08	0.15	0.48
Total chol	−0.01	0.91	−0.01	0.95
Vessel size	−0.07	0.57	−0.21	0.36
Hyperemia	−0.22	0.31	0.16	0.29

Chol = cholesterol; SBP = systolic blood pressure.

changes, including arterial collagen degeneration, loss of elastin and reduced vascular compliance (21,22). As with previous studies of endothelial changes with age, almost all such studies have been performed in white subjects living in developed countries. We (12) and others (6,11) have previously documented a marked age-related decline in endothelium-dependent arterial dilation in white subjects. Other investigators (8,23) have demonstrated a similar pattern in Oriental (Japanese) patients with coronary disease requiring angiography; however, these were symptomatic patients with multiple vascular risk factors and most had advanced atherosclerosis. Endothelial physiology has not been investigated previously in healthy Chinese, and in this study, the investigation of subjects without known vascular risk factors has allowed an assessment of the effects of aging itself on arterial reactivity (both endothelium-dependent and independent dilation). The noninvasive test we used to assess endothelial function in this study appears to be accurate, reproducible and significantly correlated with coronary endothelial physiology; it mainly reflects nitric oxide release by the endothelium (16,24,25).

Mechanism of age-related endothelial dysfunction. The mechanism whereby aging is associated with impaired endothelial function in whites is not known; however, age-related increases in arterial wall free radical release (26), in peroxidative stress (27), in catabolism of one or more endothelium-derived relaxing factors or in release of constricting factors, alone or in combination, have been suggested (28). Changes in risk factor profiles with age may also play a role. Like others (29–31), we found age-related increases in total cholesterol and systolic blood pressure levels in both Chinese and white subjects. However, the age-related decline in endothelial function occurred only in the Caucasian but not in the Chinese adults studied. The factors responsible for the relative protection from such age-related arterial change in Chinese adults warrant further investigation. Our finding that endothelium-dependent dilation was similar in the healthy *young* adult Chinese and whites argues against a simple genetic or ethnic advantage for Chinese as the only explanation for their lesser susceptibility to age-related endothelial dysfunction. Furthermore, both the younger and the older Chinese had lipid and lipoprotein levels similar to those of their age-matched Caucasian counterparts, suggesting that differences in these measured lipids are unlikely explanations for the better arterial function in older Chinese than in whites. Although the mechanism for this observation cannot be addressed directly from this study, certain environmental factors may be important. It is possible, for example, that unmeasured lipoprotein differences, such as susceptibility to oxidation (an important influence on endothelial physiology) (32,33), may be different in Chinese; for example, southern Chinese have a high consumption of green teas, which are rich in antioxidant flavonoid compounds (34). Other important dietary differences relating to increased consumption of vegetables and fish, with lower consumption of saturated fat in the traditional Chinese diet, may be contributing to the protection observed in older Chinese arteries. Potential candidates for vascular protection in such a diet include soy protein (35) and plant phytoestrogens (36).

We (12) and others (37,38) have previously suggested that the observed postmenopausal decline in endothelial function in older women may be related to estrogen deprivation after the cessation of menses. In older Chinese women, no significant impairment of endothelium-dependent dilation was seen in this study, although their postmenopausal status was similar to that of older white women. This finding may be relevant when considering the benefits of hormone replacement after menopause, and it suggests that the effects of hormones in Chinese women should be studied separately rather than simply extrapolating results obtained in whites to this ethnic group.

Limitations of the study. The current study is limited by its cross-sectional nature. Although the ethnic groups were well matched for known vascular risk factors (no subjects had clinical features of atherosclerosis, diabetes or hypertension, and all were matched for age, gender and nonsmoking status), it is possible that unmeasured differences between the groups may have been present. Analysis of the study results was also carefully matched between centers; the studies were carried out and analyzed by the same investigators in both countries, and the analyzers were unaware of subject identity during scan measurement. We also attempted to minimize differences between centers in any recruitment bias, which is inherent in the use of consenting volunteers (e.g., literacy, willingness to participate in health research); therefore, any selection bias present might be expected to be comparable between the ethnic groups. Another potential form of selection bias is the recruitment of older subjects, who must have survived until age $\geq$55 years for inclusion in the groups of older adults. This effect is likely to be numerically small (population mortality in both Australia and China is $<$10% by age 55 years) and, if present, would result in apparently improved arterial function in whites, in whom premature vascular death is more common than in China (in this study, the opposite finding was observed).

Despite these limitations, there was a highly significant decrease in endothelium-dependent dilation in the older white subjects compared with findings in both young whites and older Chinese subjects. Therefore, it is likely that there is less age-related decline in endothelium-dependent dilation in Chinese than in white subjects, although some age-related decline in endothelium-dependent dilation in Chinese adults $>$70 years old cannot be excluded. In this study, we also observed a greater degree of peak reactive hyperemia after cuff occlusion and release in Chinese than in whites, both young and old. The reasons for this difference are unclear and may relate to different small vessel densities or metabolic responses, or both. Despite this difference, the hyperemic response was high in all groups ($>$400%), the endothelium-dependent dilation response was not correlated with the degree of hyperemia observed and on multivariate analysis, the differences in age effect on endothelium-dependent dilation between the two ethnic groups studied were independent of the hyperemia differences.

Conclusions. Cardiovascular disease is the most common cause of death in developed nations but is much less prevalent in China (39). Between young adult life, when endothelial physiology may be similar in healthy white and Chinese subjects, and middle age, whites but not Chinese have manifested an impairment of arterial endothelial physiology. Elucidation of the environmental factors that may protect Chinese subjects from an age-related decline in endothelial function may be important in attempts to retard arterial disease progression in all subjects.

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