Protective Effect of Chronic Garlic Intake on Elastic Properties of Aorta in the Elderly

Kerstin Breithaupt-Grögler, MD; Michael Ling, MD;
Harisios Boudoulas, MD, PhD; Gustav G. Belz, MD, PhD

Background Epidemiological studies have suggested that garlic may have protective effects against cardiovascular diseases. We undertook this cross-sectional observational study to test the hypothesis that regular garlic intake would delay the stiffening of the aorta relating to aging.

Methods and Results We studied healthy adults (n=101; age, 50 to 80 years) who were taking ≥300 mg/d of standardized garlic powder for ≥2 years and 101 age- and sex-matched control subjects. Pulse wave velocity (PWV) and pressure-standardized elastic vascular resistance (EVR) were used to measure the elastic properties of the aorta. Blood pressures, heart rate, and plasma lipid levels were similar in the two groups. PWV (8.3±1.46 versus 9.8±2.45 m/s; $P<.0001$) and EVR (0.63±0.21 versus 0.9±0.44 $m^2 \cdot s^{-2} \cdot mm\ Hg^{-1}$; $P<.0001$) were lower in the garlic group than in the control group. PWV showed significant positive correlation with age (garlic group, $r=.44$; control group, $r=.52$) and systolic blood pressure (SBP) (garlic group, $r=.48$; control group, $r=.54$). With any degree of increase in age or SBP, PWV increased less in the garlic group than in the control group ($P<.0001$). ANCOVA and multiple regression analyses demonstrated that age and SBP were the most important determinants of PWV and that the effect of garlic on PWV was independent of confounding factors.

Conclusions Chronic garlic powder intake attenuated age-related increases in aortic stiffness. These data strongly support the hypothesis that garlic intake had a protective effect on the elastic properties of the aorta related to aging in humans. **(*Circulation.* 1997;96:2649-2655.)**

Key Words • aorta • arteriosclerosis • elasticity • garlic • waves

Ecological studies have suggested an inverse relationship between nutritional garlic intake and cardiovascular mortality; this has been attributed to a protective effect of garlic against cardiovascular diseases.[1,2] Although it has been reported that garlic intake may have beneficial effects on blood pressure, blood lipids, and blood coagulation factors, the precise mechanism or mechanisms responsible for the effect or effects remain to be defined.[1-4]

It is well appreciated that the aorta does not only serve a conduit function but also plays an important role in the modulation of left ventricular performance, myocardial perfusion, and arterial function throughout the entire cardiovascular system.[5-9] Several indices have been used to evaluate the elastic properties of the aorta in humans; PWV is a simple, noninvasive, highly reproducible index that can be used to measure elastic properties of the aorta. Increased PWV is associated with increased aortic stiffness, and vice versa.[10]

Elastic properties of the aorta decrease with age even in the absence of underlying cardiovascular pathology.[11,12] It was hypothesized that if garlic had any protective effect against cardiovascular diseases related to aging, regular garlic intake would delay the stiffening of the aorta related to aging. The present study was undertaken to test this hypothesis in an observational, cross-sectional design using a matched-pairs technique in healthy individuals aged 50 to 80 years.

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From the Centre for Cardiovascular Pharmacology, ZeKaPha GmbH (K.B.-G., M.L., G.G.B.), Mainz, Germany, and Division of Cardiology (H.B.), Ohio State University, Columbus, Ohio.

Correspondence to Prof Gustav G. Belz, MD, PhD, FAAC, Zentrum für Kardiovaskuläre Pharmakologie, Mathildenstraße 8, 55116 Mainz, Germany.

Methods

Study Population

The study was performed according to the revised Declarations of Helsinki, and the protocol was approved by an independent ethics committee. Written informed consent was obtained from all subjects before the study. Healthy, nonsmoking individuals with an age range of 50 to 80 years and a history of regular garlic intake (≥300 mg powder preparation/d for ≥2 years immediately preceding the study) were included in the garlic group. Healthy individuals without regular garlic intake, who were age (±5 years) and sex matched with similar body weight (±10%), were used as control subjects. Two hundred two subjects were studied; none were endurance-trained athletes. All subjects were Caucasians who lived within the same geographic area. The garlic group included 101 subjects (52 women and 49 men; mean age, 63.1 years), and the control group included 101 subjects (52 women and 49 men; mean age, 62.4 years) (Table). Garlic users reported ingesting an average of 4.6 (range, 3 to 9) 100-mg garlic tablets for an average of 7.1 years (range, 2 to 16 years; median, 5.7 years). Subjects receiving regular treatment with medications that may alter the elastic properties of the aorta (eg, ACE inhibitors, direct vasodilators, lipid-lowering agents) as well as garlic intake were excluded from the study. Specific questions were asked that were related to casual performance of sports and composition of diet in general. Physical examination was within normal limits in all studied subjects.

Study Procedure

Carotid and femoral artery pressure pulse waves were recorded simultaneously using a noninvasive sphygmographical technique; PWV (m/s) was calculated from the time delay in pulse pressure waves from the carotid to the femoral artery divided by the length of arterial segment (distance between

Selected Abbreviations and Acronyms

DBP = diastolic blood pressure
EVR = elastic vascular resistance
MAP = mean arterial blood pressure
PWV = pulse wave velocity
SBP = systolic blood pressure

transducers), as we previously described.[13-15] SBP and DBP were obtained using a standard mercury sphygmomanometer. Measurements were performed with subjects in the supine position at rest and during isometric handgrip exercise at 30% of individual maximal capacity. The average values of three recordings of PWV and blood pressure at rest and the measurement at 3 minutes of handgrip exercise were used for further analysis. EVR, a pressure-standardized index of aortic stiffness, was calculated using the formula $EVR=(PWV)^2/MAP$ ($m^2 \cdot s^{-2} \cdot mm\ Hg^{-1}$).[15] MAP was calculated using the formula $MAP=DBP+0.43(SBP-DBP)$.[16]

In subsets of 24 subjects from each group the effects of wave reflection on pulse height were studied. Analyses of carotid wave contours were performed as described by O'Rourke et al[17] and augmentation of the late systolic peak was determined as percentage of the total pulse height.

Body mass index was calculated as the ratio of weight to the height in the second power (weight/height^2). Total cholesterol, HDL cholesterol, and serum triglyceride levels were determined with automatic analyzers; LDL cholesterol was calculated according to the Friedewald formula as follows: LDL=total cholesterol−HDL cholesterol−(triglycerides/5).

Statistical Analysis

Statistical analyses included standard descriptive measures, linear regressions, and correlations (least-squares fitting procedure according to Marquardt[18] modified by Siegel and Klüßendorf [unpublished data; Department of Physiology, FU University of Berlin, Germany, 1996]), multiple regression analysis with backward and forward elimination procedures, and ANCOVA. Wilcoxon test and χ^2 distribution were used to determine statistical differences between groups. The Student's *t* test with Cochran and Cox approximation was done to analyze subsets of data. Statistical significance was accepted at the $\alpha=5\%$ level except for multiple regression elimination procedures, when an $\alpha=10\%$ boundary was set to minimize type II errors.

Results

SBP and heart rate at rest and during handgrip exercise were not statistically different between the two groups (Table); likewise, HDL and LDL were not statistically different (Table). Both groups were receiving a similar regional German diet. Casual participation in sports was reported by 43% of garlic users and 38% of control subjects.

PWV was significantly lower in the garlic group than in the control group at rest and during handgrip isometric exercise ($P<.0001$; Table, Fig 1). Likewise, the standardized EVR values at rest and during isometric handgrip exercise were significantly different between the groups ($P<.0001$; Table, Fig 1).

The difference in PWV between the two group means was 1.49 m/s. This difference, however, was smaller in the younger and greater in the older age groups. Thus, the mean difference between garlic users and controls was 0.53 m/s in the age group of 50 to 59 years ($P=.06$), 1.93 m/s in the age group of 60 to 69 years ($P=.0001$), and 2.21 m/s in the age group of 70 to 80 years ($P=.0016$, Fig 2).

The difference in EVR at rest between the two group means was 0.27 $m^2 \cdot s^{-2} \cdot mm\ Hg^{-1}$. This difference, like PWV, was smaller in the younger and greater in the older age groups. Thus, the difference between garlic users and controls was 0.08 $m^2 \cdot s^{-2} \cdot mm\ Hg^{-1}$ in the age group of 50 to 59 years ($P=.06$), 0.36 $m^2 \cdot s^{-2} \cdot mm\ Hg^{-1}$ in the age group of 60 to 69 years ($P=.0001$), and 0.41 $m^2 \cdot s^{-2} \cdot mm\ Hg^{-1}$ in the age group of 70 to 80 years ($P=.0004$).

A good correlation was found between PWV and age in both groups (garlic group, $r=.44$; control group, $r=.52$). The slope of the lines relating PWV and age was different between the two groups; with any degree of increase in age, the PWV increased less in the garlic group than in the control group ($P<.0001$, Fig 3). A similar correlation was found between age and the blood pressure–standardized index of EVR (garlic group, $r=.44$; control group, $r=.48$). Again, the regression line

Table 1. Description of Collectives (Demographics, Hemodynamic, and Laboratory Data)

	Garlic Group			Control Group		
	Median	Mean	SD	Median	Mean	SD
Age, y	62.0	63.1	7.7	62.0	62.4	7.2
Height, m	1.70	1.70	0.08	1.70	1.71	0.07
Body mass index, $kg \cdot m^{-2}$	24.5	24.8	2.8	24.7	25.0	2.6
Cholesterol, mmol/L	6.02	6.22	1.07	6.04	6.11	1.12
HDL, mmol/L	1.45	1.45	0.46	1.37	1.43	0.49
LDL, mmol/L	4.06	4.12	0.98	4.06	4.07	1.04
Triglycerides, mmol/L	1.29	1.44	0.92	1.13	1.39	0.83
SBP_{rest}, mm Hg	143.0	143.4	16.2	142.0	142.5	12.4
DBP_{rest}, mm Hg	90.0	88.5	6.6	90.0	89.1	6.3
HR_{rest}, min^{-1}	61.4	62.7	8.8	59.5	61.1	9.8
PWV_{rest}, m/s	8.35	8.31*	1.46	9.31	9.80	2.45
EVR_{rest}, $m^2 \cdot s^{-2} \cdot mm\ Hg$	0.59	0.63*	0.21	0.8	0.9	0.44
SBP_{stress}, mm Hg	162.0	162.1	17.1	164	163.7	13.5
DBP_{stress}, mm Hg	100	99.8	8.2	102	102.5	7.5
HR_{stress}, min^{-1}	68.5	69.9	10.9	67.5	68.2	9.0
PWV_{stress}, m/s	9.16	9.53*	2.05	10.62	11.19	3.21
$EVRL_{stress}$, $m^2 \cdot s^{-2} \cdot mm\ Hg^{-1}$	0.66	0.75*	0.32	0.87	1.05	0.72

*$P<.0001$ compared with control. HR indicates heart rate.

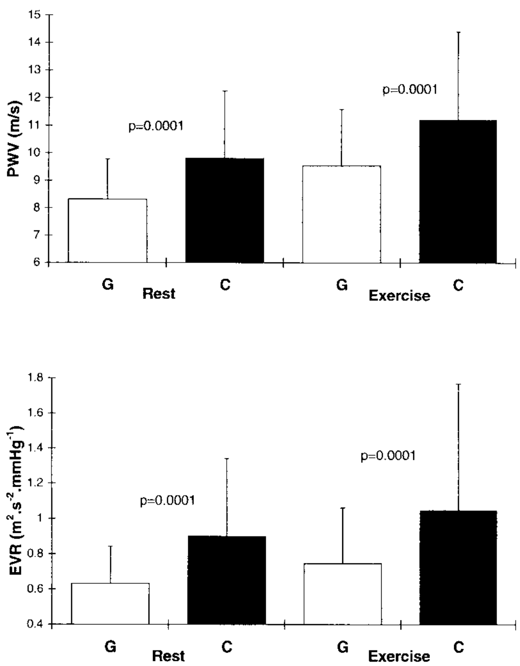

FIG 1. PWV and EVR at rest and during isometric exercise in the garlic (G) and control (C) groups (mean±SD). Note that PWV and EVR were smaller at rest and during exercise, an indication that the elastic properties of the aorta were better maintained in the garlic group.

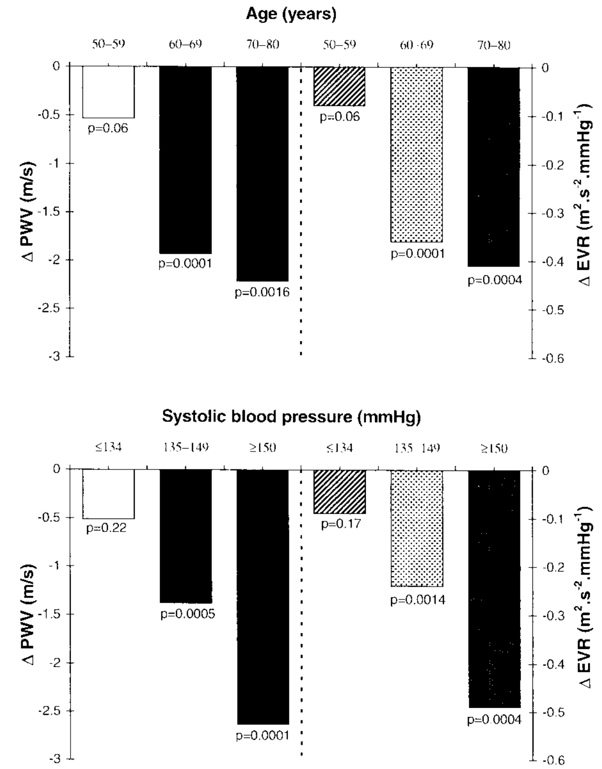

FIG 2. Top, Differences in group mean PWV (left) and EVR (right) for different age groups. Bottom, Differences in group mean PWV (left) and EVR (right) for different SBP groups. The differences are greater in the older ages and individuals with higher SBPs.

was flatter in the garlic group than in the control group ($P<.0001$, Fig 3).

A good correlation was also present between PWV and SBP in both groups (garlic group, $r=.48$; control group, $r=.54$; Fig 4). The slope of the lines, however, relating SBP and PWV differed between the two groups. Thus, for any degree of increase in blood pressure, the increase in PWV was smaller in the garlic group than in the control group ($P<.0001$, Fig 4). Correlations were also found between EVR (MAP-standardized index) and SBP in both groups (garlic group, $r=.26$; control group, $r=.42$), with the correlation coefficients somewhat smaller than for PWV. The slope of the lines, however, relating EVR and SBP differed between the two groups. Thus, for any degree of increase in blood pressure, the increase in EVR was smaller in the garlic group than in the control group ($P<.0001$, Fig 4).

The difference in PWV between the two group means was smaller in the lower-pressure and greater in the higher-pressure groups. Thus, the difference between the two groups was 0.51 m/s in individuals with SBPs of ≤134 mm Hg ($P=.22$), 1.38 m/s in individuals with SBPs of 135 to 149 mm Hg ($P=.0005$), and 2.63 m/s in individuals with SBPs of ≥150 mm Hg ($P=.0001$, Fig 2). Likewise, the difference in EVR between the two group mean values was smaller in the lower-pressure and greater in the higher-pressure groups. Thus, the difference between the two groups was 0.09 $m^2 \cdot s^{-2} \cdot mm\ Hg^{-1}$ in individuals with SBP of ≤134 mm Hg ($P=.17$), 0.24 $m^2 \cdot s^{-2} \cdot mm\ Hg^{-1}$ in individuals with SBP of 135 to 149 mm Hg ($P=.0014$), and 0.49 $m^2 \cdot s^{-2} \cdot mm\ Hg^{-1}$ in individuals with SBP of ≥150 mm Hg ($P=.0001$).

Similar correlations were found during handgrip exercise test between age and PWV (garlic group, $r=.37$; control group, $r=.53$), age and EVR (garlic group, $r=.38$; control group, $r=.45$), and SBP and PWV (garlic group, $r=.40$; control group, $r=.34$). Again, with any degree of increase in age or SBP, the increase in PWV or EVR was less in the garlic group than in the control group ($P<.0001$).

The augmentation of the late systolic peak of the carotid pulse was diminished in garlic users (10.3%; 95% confidence interval, 4.0 to 16.5) compared with the control group (20.0%; 95% confidence interval, 16.8 to 23.2; $P<.01$).

Garlic users were subdivided in those with reported doses of 300 mg/d (n=36), 400 mg/d (n=21), and 600 mg/d (n=39) garlic powder. The remaining 5 patients were taking 500 or 900 mg/d. Analysis of the relations between PWV and age, PWV and pressure, EVR and age, and EVR and pressure for these three subgroups did not reveal a dose effect between garlic use and alterations in aortic stiffness associated with aging and blood pressure.

Multiple regression analyses for both collectives revealed age and SBP as the most important confounders of PWV among all variables tested (ie, age, blood pressure, heart rate, body mass index, and serum lipids and subfractions); with these influences taken into account as well as that of casual participation in sports, ANCOVA results revealed that garlic had exerted its influence completely independent of confounding factors.

Discussion

In the present study, it was demonstrated for the first time that in apparently healthy nonsmoking adults with

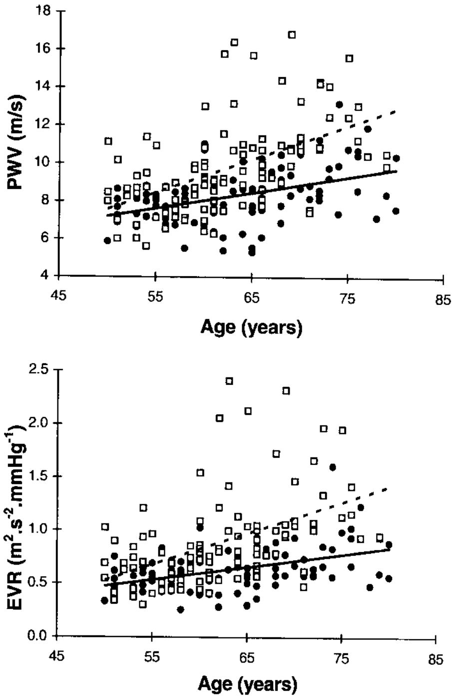

FIG 3. Top, Relationships between age and PWV in the garlic users (●) and control subjects (□). The slope of the lines relating age and PWV was different between the two groups ($P<.0001$). The linear regression line was less steep in the garlic group than in the control group; garlic group: PWV=0.08 (SD, 0.017) age+3.03 (SD, 1.081); control group: PWV=0.18 (SD, 0.029) age−1.25 (SD, 1.822). Bottom, Relationships between age and EVR in the garlic users (●) and control subjects (□). Again, the regression line was less steep in the garlic group than in the control group ($P<.0001$); garlic group: EVR=0.01 (SD, 0.002) age−0.12 (SD, 0.156); control group: EVR=0.03 (SD, 0.005) age−0.95 (SD, 0.338).

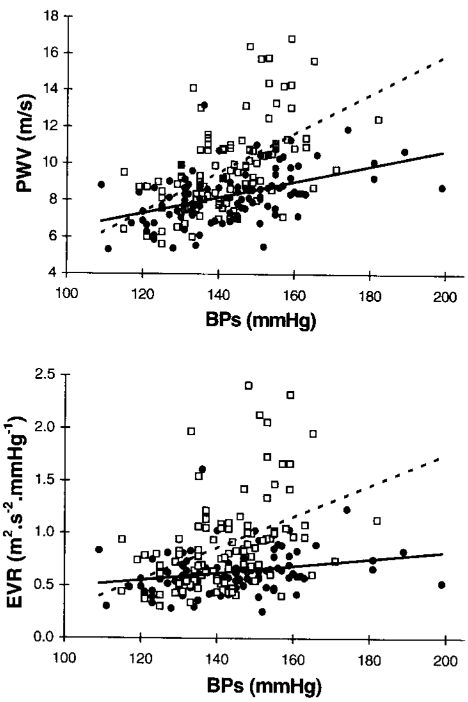

FIG 4. Top, Relationships between SBP and PWV in the garlic users (●) and control subjects (□). The slopes of the lines relating SBP and PWV was different between the two groups ($P<.0001$). The linear regression line was less steep in the garlic group than in the control group; garlic group: PWV=0.04 (SD, 0.008) SBP+2.18 (SD, 1.149); control group: PWV=0.11 (SD, 0.017) SBP−5.47 (SD, 2.377). Bottom, Relationships between SBP and EVR in the garlic group (●) and the control group (□). Again, the regression line was less steep in the garlic group than in the control group ($P<.0001$); garlic group: EVR=0.003 (SD, 0.0013) SBP+0.15 (SD, 0.181); control group: EVR=0.015 (SD, 0.0032) SBP−.23 (SD, 0.464).

an age range of 50 to 80 years, chronic garlic intake of a standardized powder preparation was associated with a decrease in PWV and blood pressure–standardized index of EVR compared with age- and sex-matched control subjects. The data suggested that the elastic properties of the aorta were maintained better in the garlic group than in the control group. Thus, the detrimental effects of age on the elastic properties of the aorta were blunted in the garlic users compared with the control subjects.

The present results confirmed previous observations in which the PWV correlated positively with age.[11,12,16,19-21] This correlation was seen in both groups. The slope of regression lines, however, relating age and PWV were different in the two groups. For any degree of increase in age, the PWV was less in the garlic group than in the control group. The difference in PWV between garlic users and controls was greater in the older than in the younger age subgroups. This might well reflect the relatively normal elastic properties of the aortic wall in younger individuals with PWVs of 7 to 8 m/s. For this reason, the effect of garlic on the elastic properties of the aorta was more obvious in the advanced age group.

Factors Determining Aortic Function

Any change in structure of the arterial wall may result in abnormal aortic function.[5,10,22-26] In experimental animals, changes of the arterial wall structure during the progression and regression of atherosclerosis paralleled indices of aortic elastic properties. Regression of atherosclerosis resulted in a decrease in PWV, and vice versa.[27] Similar findings have been reported during the development and treatment of arterial hypertension.[15,28,29] Abnormal aortic function, however, may be present in cases in which structural abnormalities of the aortic wall cannot be precisely defined with contemporary technology. For example, acute changes of blood supply to the aortic wall due to a decrease in vasa vasorum flow may result in aortic dysfunction.[5,30]

Endothelium-derived relaxant factor (nitric oxide), endothelin, atrial natriuretic peptides, catecholamines, and prostaglandins may alter the elastic properties of the aorta directly through their effects on the smooth muscle of the aortic wall and indirectly by their effects on vasa vasorum flow. In addition, the autonomic nervous system may play a significant role in the determination of the aortic wall function through a direct effect on the smooth muscle, vasa vasorum flow, or neurohumoral activation.[31-34]

Factors That May Account for Differences in Elastic Properties Between the Two Groups

PWV and its derivative EVR were used as indices of the elastic properties of the aorta in the present study. It is known, however, that arterial pressure may have some effect on these indices,[11,12,15,35,36] yet in the present study, blood pressures were similar in the two groups. Furthermore, for any degree of increase in blood pressure, the elastic properties of the aorta were better maintained in the garlic group than in the control group. Thus, the observed differences in PWV cannot be attributed to differences in blood pressure. In addition, determination of the pressure-standardized stiffness index EVR has demonstrated similar results.

Pharmacological agents, cigarette smoking, and composition of general diet may change the elastic properties of the aorta.[10,15,29,37-39] To avoid the effects of these factors, only healthy individuals, not those receiving therapy with cardiovascular drugs and nonsmokers who lived within the same geographic area, with similar nutritional habits were included in the study.

It is known that increased cholesterol has detrimental effects on the arterial elastic properties; cholesterol and aortic stiffness have been shown to be positively correlated.[5,19,20,40,41] Some studies have suggested that garlic intake may decrease plasma cholesterol.[2,3,42] Differences in cholesterol, however, cannot account for differences in the elastic properties of the aorta because serum lipid levels were similar in the two groups. Furthermore, in a recent double-blind, placebo-controlled, cross-over study of 28 patients with hypercholesterolemia, the administration of 900 mg/d garlic powder for 3 months had no effect on plasma cholesterol.[43]

Possible Mechanisms Involved in the Vasoprotective Effects of Garlic

Recent data suggested that endothelium-derived relaxant factor (nitric oxide) regulates vascular homeostasis by controlling vascular resistance, blood pressure, cell-cell contact, and proliferation.[44,45] Fröhlich et al[46] demonstrated that stimulation of endogenous nitric oxide formation increased nutritive muscular capillary blood flow in patients with peripheral occlusive disease. In addition, the same group presented data showing that activation of nitric oxide synthetase in cholesterol-fed rabbits had a stronger inhibitory effect on the progression of atherosclerosis than cholesterol-lowering therapy with lovastatin.[47]

Incubation of human tissues with garlic extracts has been shown to increase nitric oxide synthase activity.[48] Increased nitric oxide synthase activity may facilitate endothelium-dependent smooth muscle relaxation through the intracellular second messenger cAMP, which in turn may increase vasa vasorum flow. Vasa vasorum flow contributes to the nutrition of the outer layers of the thoracic aorta, and its impairment induced structural changes of the aortic wall with deterioration of the elastic aortic properties.[5,30] It is also known that vasa vasorum flow is decreased in advancing age.[34] Thus, garlic intake may possibly restore impaired endothelium function by nitric oxide synthase activation and so maintain the elastic properties of the aorta.

Other studies also have suggested that regular garlic intake may have an inhibitory effect on platelet aggregation, increase fibrinolytic activity, and inhibit atherosclerotic plaque formation.[1,2,49-51] Nevertheless, the present study demonstrated that garlic delays the stiffening of the aorta relating to aging. The precise mechanism or mechanisms of this effect of garlic on the elastic properties of the aorta remain to be defined.

Study Limitations

This study does not have a randomized, prospective design but rather an epidemiological and cross-sectional scope. However, we used matched pairs, and as with case-control studies, these designs are appropriate for interventions with long-latency studies on dietary effects. These designs may have potential for bias in selection of participants and relevant confounding by unknown factors.[52] We tried to keep confounding factors as low as possible and to eliminate their influence through the use of ANCOVA. PWV and EVR differed significantly between the garlic and control groups regardless of whether the influence of confounding variables was taken into account.

The fact that the effect of garlic on the elastic properties of the aorta was not dose related may simply reflect that the maximal effect (ceiling) had already been reached with the lowest garlic dose reported (300 mg/d). In addition, it should be taken into account that the reported dosage range is narrow and thus not well suited for judgment of dose-effect relations. Finally, these data rely on subjects' reports and may not be quite precise.

There also are limitations related to the method used to assess elastic properties of the aorta. Blood pressure may affect PWV, but in this study, blood pressure was almost the same in the two groups. Furthermore, the same differences in the elastic properties of the aorta were found when an index that was less dependent on blood pressure index (EVR) was used.

Clinical Implications

Under normal conditions, a large proportion of the left ventricular stroke volume is stored in the aorta during left ventricular systole, whereas during diastole, the stored blood flows into periphery.[10,16] This function of the aorta is important for the maintenance of blood flow and pressure throughout the cardiac cycle. Aortic storage capacity is diminished or lost in different disease states and in the elderly.[5,11,22-26]

When the pulse wave reaches the periphery, it returns back to the ascending aorta. Normally the reflecting waves reach the ascending aorta early in diastole; this results in the formation of the diastolic wave. Reflecting waves that reach the aortic valve early in diastole facilitate coronary blood flow. When the elastic properties of the aorta are diminished and the PWV increases, the reflecting waves from the periphery return earlier into the ascending aorta, fuse with the systolic part of the pulse, and result in an increase in pulse pressure, a late systolic peak in the pulse, and the disappearance of the diastolic wave.[17,53] Matching the slower PWV in garlic users, analyses of the carotid wave contours demonstrated that augmentation of the late systolic peak was also decreased compared with control subjects. Late systolic augmentation increases left ventricular work. Left ventricular–vascular coupling is an important determinant of left ventricular performance. In patients with left ventricular dysfunction without appropriate adaptation of the vasculature, overall circulatory performance may not improve and in fact may be diminished despite positive inotropic interventions.[5,6,54]

Aortic function is an important determinant of myocardial perfusion. Indeed, experimental studies have indicated that decreased aortic distensibility has a detrimental effect on the dynamics of coronary flow and has an aggravating effect on myocardial ischemia in the presence of coronary artery stenosis.[7,8,55]

Augmentation of the pulse pressure in the stiff aorta will result in an increase in diastolic–systolic expansion of the peripheral arteries and an increase in maximal blood velocity in the arteries during systole; this increased pulsatile stress will promote the development of vascular damage. Thus, a protective effect of garlic on the elastic properties of the aorta may provide an explanation of the protective effects of garlic against cardiovascular diseases.

Conclusions

The results of this cross-sectional observational study suggested for the first time that regular long-term garlic powder intake attenuated age- and pressure-related increases in aortic stiffness. These garlic-related effects might be mediated by nitric oxide synthase activation and subsequent restoration of impaired endothelium function. It is well appreciated that the aorta plays an important role modulating left ventricular function, myocardial perfusion, and arterial function throughout the cardiovascular system. Thus, the effect of garlic in maintaining the elastic properties of the aorta in advanced age provides insight into the mechanism or mechanisms of possible cardioprotective effect of garlic.

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