Ascorbic acid does not affect large elastic artery compliance or central blood pressure in young and older men

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Eskurza, Iratxe, Kevin D. Monahan, Jed A. Robinson, and Douglas R. Seals. Ascorbic acid does not affect large elastic artery compliance or central blood pressure in young and older men. Am J Physiol Heart Circ Physiol 286: H1528–H1534, 2004; 10.1152/ajpheart.00879.2003.—Large elastic artery compliance is reduced and arterial blood pressure (BP) is increased in the central (cardiothoracic) circulation with aging. Reactive oxygen species may tonically modulate central arterial compliance and BP in humans, and oxidative stress may contribute to adverse changes with aging. If so, antioxidant administration may have beneficial effects. Young (Y; 26 ± 1 yr, mean ± SE) and older (O; 63 ± 2 yr, mean ± SE) healthy men were studied at baseline and during acute (intravenous infusion; Y: n = 13, O: n = 12) and chronic (500 mg/day for 30 days; Y: n = 10, O: n = 10) administration of ascorbic acid (vitamin C). At baseline, peripheral (brachial artery) BP did not differ in the two groups, but carotid artery compliance was 43% lower (1.2 ± 0.1 mm 2 /mmHg × 10 −1 vs. 2.1 ± 0.1 mm 2 /mmHg × 10 −1, P < 0.01) and central (carotid) BP (systolic: 116 ± 5 vs. 101 ± 3 mmHg, P < 0.05, and pulse pressure: 43 ± 4 vs. 36 ± 3 mmHg, P = 0.16), carotid augmentation index (AIx; 27.8 ± 7.8 vs. 20.0 ± 6.6%, P < 0.001), and aortic pulse wave velocity (PWV; 950 ± 88 vs. 640 ± 38 cm/s, P < 0.01) were higher in the older men. Plasma ascorbic acid concentrations did not differ at baseline (Y: 71 ± 5 vs. O: 61 ± 7 μmol/l, P = 0.23), increased (P < 0.001) to supraphysiological levels during infusion (Y: 1.240 ± 57 and O: 1.056 ± 83 μmol/l), and were slightly elevated (P < 0.001 vs. baseline) with supplementation (Y: 96 ± 5 μmol/l vs. O: 85 ± 6). Neither ascorbic acid infusion nor supplementation affected peripheral BP, heart rate, carotid artery compliance, central BP, carotid AIx, or aortic PWV (all P > 0.26). These results indicate that the adverse changes in large elastic artery compliance and central BP with aging in healthy men are not 1) mediated by ascorbic acid-sensitive oxidative stress (infusion experiments) and 2) affected by short-term, moderate daily ascorbic acid (vitamin C) supplementation.

arterial stiffness; vitamin C; antioxidants; human aging

ONE OF THE MOST physiologically and clinically important changes that occurs with cardiovascular (CV) aging is a progressive reduction in the compliance (increase in stiffness) of the large elastic arteries in the central (i.e., cardiothoracic) circulation (e.g., the proximal aorta and carotid artery) (33, 35, 50). This process leads to several potentially adverse changes in CV structure and function including increases in central arterial blood pressure (BP), arterial intima-media thickening, increases in aortic impedance, left ventricular remodeling, reduced diastolic function, and decreased baroreflex responsiveness (28, 34, 35, 43, 44, 50). Indeed, reduced large elastic artery compliance is an independent risk factor for future CV disease (CVD) (25, 32).

Structural changes in the extracellular matrix of the vascular wall including increases in collagen content and cross-linking as well as fragmentation of elastin are important mechanisms underlying reductions in large elastic artery compliance with aging (33, 35). However, changes in factors that modulate vascular smooth muscle cell tone also affect large artery compliance (33, 35, 47).

Reactive oxygen species (ROS) are one such factor that may modulate central large elastic artery compliance in humans (45, 59). These effects may be mediated by reducing the bioavailability of nitric oxide (NO), a potent vasodilator released from the vascular endothelium (5, 33, 35, 52). Indeed, there is evidence that NO tonically enhances large artery compliance (13). Moreover, ROS could modulate the compliance of these arteries by augmenting the synthesis and release of endothelin-1 (4), a powerful endothelium-derived vasoconstrictor factor, and/or by indirectly increasing local vascular renin-angiotensin system bioactivity (20, 36). ROS may also have direct contraction-stimulating effects on vascular smooth muscle cells (30). Oxidative stress, i.e., excessive bioavailability of ROS, develops with aging (32, 57a, 49) and, therefore, could produce increased vascular smooth muscle tone-mediated reductions in arterial compliance in older adults.

The physiological effects of ROS and, therefore, oxidative stress can be revealed by administration of antioxidants such as ascorbic acid (vitamin C) (29). A change in physiological function with ascorbic acid should reflect the presence of a tonic influence of ROS bioactivity. Administration of ascorbic acid has been reported to reduce the augmentation index (AIx) derived from peripheral artery pulse wave analysis, an indirect measure of arterial stiffness, in both healthy young men (59) and in middle-aged and older patients with Type II diabetes (45). However, the effects of ROS/oxidative stress on proximal large elastic artery compliance and central BP have not been directly determined in humans in general and in older adults in particular.

Finally, if acute administration of ascorbic acid can increase large elastic artery compliance and, as a result, lower central BP, especially in older adults, it is possible that daily supplementation of ascorbic acid could be used therapeutically to sustain these improvements. However, currently no information is available on this possibility.

In the present investigation, we infused ascorbic acid to acutely raise plasma concentrations to supraphysiological levels in young and older healthy men to determine whether...
oxidative stress tonically modulates large elastic artery compliance and central BP. We then supplemented ascorbic acid oral intake for 30 days to identify any possible therapeutic benefits.

METHODS

Subjects

A total of 25 healthy men participated in protocol 1 (acute infusion of ascorbic acid): 13 young (aged 18–30 yr) and 12 older (aged 60–79 yr); 20 of these subjects (10 young and 10 older) also completed protocol 2 (chronic supplementation). Subjects were sedentary, nonobese, normotensive (brachial BP < 140/90 mmHg), and free of overt cardiovascular disease as assessed by medical history, physical examination, blood chemistry, and resting and exercise (older men only) ECG. Candidates who used antioxidants (vitamin C and E or any other type) within 6 wk of the time of recruitment or who were taking medications were excluded from participation. All subjects gave their written informed consent to participate. All procedures were revised and approved by the Human Research Committee of the University of Colorado (Boulder, CO).

General Experimental Procedures

Before the main experimental sessions, subjects fasted for 12 h. During these sessions subjects were positioned supine and instrumented with an intravenous catheter in the left arm for ascorbic acid infusions and acquisition of blood.

Carotid Artery Compliance and BP

Carotid arterial compliance was assessed noninvasively as previously described in detail (54). Briefly, common carotid artery diameters and contralateral carotid artery BP were simultaneously assessed by high-resolution ultrasonography (Toshiba 6000 Power Vision) and applanation tonometry, respectively. Carotid artery diameters were measured ~2 cm proximal to the carotid bulb with the transducer placed at a 90° angle to the vessel. Images were recorded on super-VHS videocassettes for subsequent off-line analysis with image analysis software. Maximal diameters (i.e., systolic expansion) and minimal diameters (e.g., diastolic relaxation) were measured based on carotid BP waveforms. All image analyses were performed by the same investigator (I. Eskurza), who was blinded to the identity of the subjects. Applanation tonometry was performed over the contralateral carotid artery with a pencil-type probe connected to a high-fidelity strain-gauge transducer (TCB-500, Millar Instruments). This technique provides waveforms with the same harmonic content as those obtained invasively in humans (31). Because this technique depends on hold-down pressure, to determine carotid BP the brachial artery was used to calibrate carotid artery waveforms (1). Carotid artery compliance was calculated as previously described (54). The reliability of measurements of carotid artery diameter, BP, and compliance in our laboratory have been established previously, with coefficients of variation of 2, 7, and 5%, respectively (54).

Arterial Stiffness

Carotid AIx and aortic pulse wave velocity (PWV), measures of overall and proximal large elastic arterial stiffness, respectively (45), were determined as described in detail previously (53). Briefly, AIx was determined by applanation tonometry of the carotid artery, and aortic PWV was determined using transcutaneous Doppler flowmeters positioned at the aortic arch and femoral artery. The reliability of these measurements in our laboratory have been established previously, with coefficients of variation ranging from 7 to 8% (53).

Brachial Artery BP

BP was measured over the brachial artery with the use of a semiautomated device (Dynamap XL, Johnson and Johnson).

Body Composition

The percent body fat was measured using dual-energy X-ray absorptiometry (DXA-GE, Lunar; Madison, WI, software version 5.60.003).

Blood Measurements

Plasma samples were analyzed for venous ascorbic acid concentrations (14), oxidized LDL, an indirect measure of oxidative stress (26), catecholamines (48), and endothelin-1 (competitive radioimmunoassay) (37).

Protocols

Protocol 1. To determine whether ROS/oxidative stress tonically modulate central large elastic artery compliance, stiffness, and BP and contribute to adverse changes with age, measurements were obtained before (saline infusion) and after intravenous administration of a pharmacological dose of ascorbic acid (American Regent Laboratories): a priming bolus of 0.06 g/kg fat-free mass (FFM) dissolved in 100 ml saline infused at 5 ml/min for 20 min, followed by a “drip infusion” of 0.02 g/kg FFM dissolved in 30 ml saline administered over 60 min at 0.5 ml/min.

Protocol 2. To determine whether the age-associated changes in central large elastic artery compliance, stiffness, and BP can be at least partially reversed with oral ascorbic acid supplementation, subjects ingested 500 mg/day of ascorbic acid (time-release capsules, Goldline Laboratories) for 30 consecutive days as described previously (19). Chronic supplementation was started at least 72 h after the acute administration session. Adherence to the treatment was established by subject logs that were completed each day and by measuring plasma ascorbic acid concentration 2 wk after the treatment was started.

Statistical Analysis

Differences in subject characteristics between the two groups were determined by ANOVA. Repeated-measures ANOVA was used to examine the main effects of acute and chronic ascorbic acid administration. Univariate correlation analyses were performed to examine relations between variables of interest. All data are reported as means ± SE. Statistical significance was set at P < 0.05.

RESULTS

Protocol 1: Acute Ascorbic Acid Infusion

Subject characteristics. Values are shown in Table 1. The groups did not differ in height, brachial systolic or mean BP, heart rate, or plasma HDL-cholesterol, insulin, or glucose. Body weight, percent body fat, brachial diastolic BP, plasma total cholesterol, LDL-cholesterol, and plasma oxidized LDL were greater in the older men (P < 0.05).

Plasma ascorbic acid concentrations. At baseline, there were no group differences in plasma ascorbic acid concentrations (young: 71 ± 5 vs. older: 61 ± 7 μmol/l, P = 0.23). With infusion, plasma ascorbic acid concentrations increased above baseline (P = 0.0001) to supraphysiological levels in both groups (young: 1,240 ± 57 and older: 1,056 ± 83 μmol/l). Carotid artery compliance, BP, AIx, and aortic PWV. Results are presented in Fig. 1 and Table 2. Baseline carotid artery compliance was 43% lower (P < 0.01) and carotid BP (systolic: +15 mmHg, P < 0.05, and pulse pressure: +7 mmHg, P = 0.12), AIx (+48%, P < 0.001), and aortic PWV (+48%, P < 0.001) were higher in the older men. Correction of the measures of arterial compliance and stiffness for central BP
had no effect on the age-associated differences. Carotid artery diameter during diastole did not differ between the groups (Table 2). Ascorbic acid infusion had no effect on any of these CV functions.

**Plasma catecholamine and endothelin-1 concentrations.** At baseline, plasma concentrations of epinephrine were not different in the young (35 ± 12 pg/ml) and older (37 ± 12 pg/ml) men, but plasma norepinephrine (255 ± 39 vs. 138 ± 19 pg/ml) and endothelin-1 (6.8 ± 0.3 vs. 5.5 ± 0.4 pg/ml) concentrations were greater in the older men (both P < 0.05). There were no changes from these baseline values during ascorbic acid infusion (data not shown).

**Correlates of baseline arterial stiffness.** Baseline plasma norepinephrine concentrations were positively related to AIx (r = 0.61, P < 0.01) and aortic PWV (r = 0.54, P < 0.05). Baseline carotid systolic BP was positively related to AIx (r = 0.43, P = 0.06) and aortic PWV (r = 0.53, P < 0.05), and brachial systolic BP was positively related to aortic PWV (r = 0.55, P = 0.01).

**Protocol 2: Chronic Ascorbic Acid Supplementation**

**Subject characteristics.** Characteristics of the subset of subjects completing protocol 2 (10 young and 10 older) were not different from those for the overall group presented in Table 1.

**Plasma ascorbic acid concentrations.** At baseline, there were no group differences in plasma ascorbic acid concentrations for these subsets of the young and older men (young: 65 ± 5 vs. older: 60 ± 9 μmol/l, P = 0.64). Plasma concentrations of ascorbic acid measured 12 h after oral ingestion were modestly elevated compared with baseline (P < 0.01) and not different in the two groups (older: 85 ± 6 vs. young: 96 ± 5 μmol/l, P = 0.18).

**Carotid artery compliance, BP, AIx, and aortic PWV.** The same age group differences were observed at baseline for this subset of subjects as in the overall subject sample (Fig. 1 and Table 2). Chronic ascorbic acid supplementation had no effect on any of the CV functions compared with baseline (Table 3).

**Plasma catecholamine and endothelin-1 concentrations.** As in protocol 1, in these subgroups baseline plasma concentrations of norepinephrine and endothelin-1 were higher in the older men (P < 0.05), whereas plasma epinephrine concentrations did not differ. Chronic ascorbic acid supplementation had no effect on plasma concentrations compared with baseline values.

**DISCUSSION**

There are two primary new findings from this investigation. First, the results of our infusion experiments indicate that ROS, at least those sensitive to ascorbic acid, do not tonically modulate large elastic artery compliance or central BP in young and older healthy men. As a result, our findings suggest that ascorbic acid-sensitive oxidative stress does not contribute mechanistically to the adverse changes in compliance and central BP with aging. Second, consistent with these observations from our infusion experiments, we found that short-term, moderate daily ascorbic acid supplementation did not affect central arterial compliance or BP and thus does not appear to provide any therapeutic benefits even in older adults.

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**Table 1. Subject characteristics for protocol 1:**

<table>
<thead>
<tr>
<th></th>
<th>Young Men</th>
<th>Older Men</th>
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<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Age, yr</td>
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<td>63±2*</td>
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<tr>
<td>Height, cm</td>
<td>179±2</td>
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<td>Body fat, %</td>
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<td>Heart rate, beats/min</td>
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<td>Total cholesterol, mmol/l</td>
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<tr>
<td>Plasma insulin, μU/ml</td>
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<td>Plasma glucose, mmol/l</td>
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<td>Oxidized LDL-cholesterol, IU/l</td>
<td>53±4</td>
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</table>

Data are means ± SE; n, no. of subjects. SBP, systolic blood pressure (BP); DBP, diastolic BP. *P < 0.05 vs. young men.
Table 2. Protocol 1: peripheral and central BP, heart rate, and carotid artery diameters at baseline and during ascorbic acid infusion

| Protocol 1: peripheral and central BP, heart rate, and carotid artery diameters at baseline and during ascorbic acid infusion |
|---|---|---|---|
| Young Men | Older Men |
| Baseline | Ascorbic acid infusion | Baseline | Ascorbic acid infusion |
| n | 13 | 13 | 12 | 12 |
| Brachial SBP, mmHg | 115±2 | 115±2 | 120±4 | 122±3 |
| Brachial DBP, mmHg | 65±2 | 64±2 | 73±2* | 75±2* |
| PP, mmHg | 50±2 | 53±3 | 48±3 | 47±2 |
| Heart rate, beats/min | 58±2 | 56±2 | 64±2 | 53±3 |
| Carotid SBP, mmHg | 101±2 | 99±3 | 116±5* | 115±5* |
| Carotid PP, mmHg | 36±3 | 35±2 | 43±4 | 41±4 |
| Diastolic carotid diameter, mm | 6.1±0.1 | 6.1±0.1 | 6.4±0.2 | 6.4±0.2 |
| Systolic carotid diameter, mm | 6.8±0.1 | 6.8±0.1 | 6.9±0.3 | 6.9±0.2 |

Data are means ± SE; n, no. of subjects. PP, arterial pulse pressure. *P < 0.05 vs. young men.

Peripheral and Central Arterial Function and BP in Healthy Men with Aging

In the present study, carotid artery compliance was lower and measures of large artery stiffness and central BP were greater in the older compared with young men, consistent with previous findings (33, 35, 50). In contrast, peripheral BP was not different in the two age groups, confirming that the major effect of primary aging is on the large elastic arteries and systolic BP in the central circulation (33, 35, 50). Indeed, although peripheral systolic BP increases with age in the general adult population (33, 35, 50), we have demonstrated previously that peripheral large artery stiffness and systolic BP are not increased in rigorously screened healthy older men in whom elevations in central systolic BP are observed (44, 54, 55).

Role of ROS/Oxidative Stress in Large Elastic Artery Compliance and Central BP in Young and Older Healthy Men

At least three lines of evidence support the likelihood that the acute ascorbic acid infusion used in the present study reduced ROS/oxidative stress, particularly in our older subjects. First, it has been demonstrated that the plasma concentrations of ascorbic acid achieved during the infusions in the present study scavenge superoxide anions in vitro (29). Second, our laboratory recently demonstrated that the same intravenous infusion of ascorbic acid as used in the present study decreases plasma isoprostanes, a biomarker of lipid oxidation-associated oxidative stress, in a group of older healthy men similar to those studied here (2). Finally, coadministration of ascorbic acid restores impaired endothelium-dependent vasodilation in older humans via a NO-dependent mechanism (52). Moreover, recent findings from our laboratory show that the same intravenous infusion of ascorbic acid as used in the present study restores the impaired large artery flow-mediated dilation in healthy middle-aged and older men to levels observed in young adult controls (12).

Two previous investigations reported reductions in measures of arterial stiffness in response to ascorbic acid administration in humans, one in healthy young adults (59) and the other in middle-aged and older patients with Type 2 diabetes (45). This apparent discrepancy between the results of our study and those of earlier investigations could involve at least three factors. First, these studies used peripheral artery-derived estimates of arterial stiffness, not direct measures of central large elastic artery compliance as in the present investigation. Peripheral arteries have more vascular smooth muscle cells than the large central arteries and, therefore, are more likely to show changes in compliance in response to a stimulus that affects vascular smooth muscle cell tone. Second, in both of these previous studies, peripheral BP was reduced with ascorbic acid and therefore could have contributed to the reductions in the BP-sensitive measures of arterial stiffness used. In contrast, ascorbic acid infusion did not affect peripheral or central BP in the present investigation, and no changes in any measure of central arterial compliance or stiffness was observed in the absence of such reductions in BP. Finally, the present study involved healthy young and older men. Although oxidative stress appears to develop with age even in healthy adult humans (32, 49) and was present in our healthy older men as indicated by their higher baseline plasma oxidized LDL levels, Type 2 diabetes, particularly in middle-aged and older patients, is associated with much greater oxidative stress than that observed with primary aging (21). Ascorbic acid administration may reveal a significant contribution of oxidant stress to the marked increase in large artery stiffness associated with this more severe pathophysiological vascular state.

Effects of Chronic Oral Ascorbic Acid Supplementation in Healthy Older Men

To our knowledge, the present investigation is the first to determine the effects of daily ascorbic acid supplementation on large elastic artery compliance and central BP in healthy adults, including changes with aging. We found that daily supplementation of 500 mg of ascorbic acid for 1 mo had no effect on central arterial compliance, stiffness, or BP in either age group. These findings are not surprising given the lack of effect of supraphysiological doses of ascorbic acid on compliance and BP in our acute infusion experiments. These observations indicate that 30 days of moderate daily ascorbic acid supplementation has no obvious therapeutic efficacy for increasing large elastic artery compliance and lessening its ad-
verse cardiovascular consequences (e.g., the increase in central BP) in older adults.

**Experimental Considerations Regarding Ascorbic Acid Administration**

We chose to use ascorbic because it is one of the most potent water-soluble antioxidants in humans. Ascorbic acid scavenges superoxide anions and many other ROS, including those produced by lipid peroxidation (3, 14, 46, 58). Moreover, ascorbic acid can be acutely infused at rates that attain supraphysiologic plasma concentrations, which are known to reduce superoxide anions and increase NO bioavailability (29). Ascorbic acid consistently improves vascular endothelial function in groups with CVD risk factors and patients with clinical CVD (10, 19, 23, 25, 27, 38, 51, 56, 57). Importantly for the present study, ascorbic acid was the antioxidant used previously to determine the role of ROS/oxidative stress in modulating large elastic artery stiffness in human subjects (45, 59). Thus ascorbic acid administration is a well-established antioxidant model for reducing ROS/oxidative stress in human CV research.

In the present study, we also wanted to determine, for the first time, whether oral ascorbic acid supplementation could be used to reverse the adverse age-related changes in central BP and large elastic artery compliance. The dose (i.e., 500 mg/day) and treatment duration (30 days) were chosen on the basis that they previously had been shown to restore vascular endothelium-dependent dilation in patients with coronary artery disease (19). In addition, plasma ascorbic acid is tightly controlled by tissue transport, absorption, and excretion. When given orally, the relation between oral dose and plasma concentration is sigmoidal, and plasma is completely saturated at a dose of 400 mg/day (39, 40), with the kidney rapidly excreting any excess ascorbic acid. However, even with the use of slow-releasing tablets such as those used in the present study up to 80% of the ascorbic acid taken orally is excreted within 5 h (39). Given these facts, it is unlikely that a larger dose and/or longer period of ascorbic administration would have produced different results.

Finally, we cannot exclude the possibility that other antioxidants (e.g., vitamin E, glutathione, β-carotene, and/or superoxide dismutase) may have produced improvements in compliance and central BP. Present experimental findings, however, are mixed regarding the effect of vitamin E (and, even more so, β-carotene) on CV function (6, 11, 17, 24). Even combinations of antioxidants (normally ascorbic acid, vitamin E, and β-carotenes) when given orally at physiological doses show conflicting results on CV outcomes (18, 42). Superoxide dismutase, perhaps the most important extra- and intracellular antioxidant against superoxide anions, does not improve endothelial function in humans, probably due to lack of penetration into the vascular wall (16). We recognize that the most effective approach to acutely reducing ROS/oxidative stress would be to inhibit the sources of production. With respect to the vascular wall, NADPH oxidase, uncoupled endothelial NO synthase (eNOS) (i.e., as occurs with tetrahydrobiopterin co-factor deficiency), and xanthine oxidase are the most important sources of oxidative stress. Unfortunately, currently there is no available method to selectively inhibit superoxide anion production by NADPH oxidase, the major source of ROS, although tetrahydrobiopterin and allopurinol (a xanthine oxidase inhibitor) administration, respectively, could be used to decrease superoxide anion from uncoupled eNOS and xanthine oxidase.

**Physiological and Clinical Implications**

The reduction in large elastic artery compliance (increase in stiffness) in the central circulation with aging is one of the primary contributors to age-associated CVD-related pathophysiology (28, 34, 35, 43, 44, 50). By failing to demonstrate a clear role for oxidative stress, the present findings point in part to the importance of structural factors in determining large elastic artery compliance and central arterial BP in healthy adult humans as well as their changes with aging. These structural alterations involve changes in key extracellular matrix proteins including increases in collagen content and cross-linking as well as fragmentation of elastin (34). Other local, humoral, and perhaps neural influences on vascular smooth muscle cell tone in the arterial wall may, however, also contribute. Local influences include vascular angiotensin II and endothelin-1 bioactivity (15, 60). Indeed, in the present investigation, plasma endothelin-1 concentrations were higher in the older men. Humoral influences include circulating vasoactive factors such as renin-angiotensin system hormones, catecholamines, and atrial natriuretic peptide (7, 22). Finally, augmented sympathetic nervous system stimulation of vascular smooth muscle cell tone may have played a role in the changes in large elastic artery function with aging. We have shown the importance of augmented sympathetic α-adrenergic tone in reduced femoral artery blood flow and vascular conductance with aging in healthy adult men (8, 9). Consistent with this possibility, in the present study, baseline plasma norepinephrine concentrations were elevated in the older men and were positively related to both AIX (r = 0.61) and aortic PWV (r = 0.54).

In conclusion, the results of the present study indicate that the adverse changes in large elastic artery compliance and central BP with aging in healthy men are neither mediated by ascorbic acid-sensitive oxidative stress nor affected by short-term, moderate daily ascorbic acid (vitamin C) supplementation.

**GRANTS**

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