Ascorbic acid does not affect the age-associated reduction in maximal cardiac output and oxygen consumption in healthy adults

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Submitted 27 July 2004; accepted in final form 21 October 2004

Ascorbic acid does not affect the age-associated reduction in maximal cardiac output and oxygen consumption in healthy adults. J Appl Physiol 98: 845–849, 2005. First published October 22, 2004; doi:10.1152/japplphysiol.00790.2004.—Maximal aerobic capacity (V\(\text{O}_2\) max) decreases progressively with age, primarily because of a reduction in maximal cardiac output (Q\(\text{max}\)). This age-associated decline in Q\(\text{max}\) may be partially mediated by the powerful antioxidant ascorbic acid (vitamin C) (27).

In the present study, we have investigated the hypothesis that ascorbic acid administration would increase Q\(\text{max}\) and V\(\text{O}_2\) max in middle-aged and older adults. Our specific aim was to determine Q\(\text{max}\) and V\(\text{O}_2\) max in young and older sedentary adults at baseline and following an acute, supraphysiological dose of ascorbic acid previously shown to reduce oxidative stress (2). Finally, if acute administration of ascorbic acid can improve or restore Q\(\text{max}\) and V\(\text{O}_2\) max following chronic (30-day) oral administration of ascorbic acid.

**METHODS**

**Subjects.** We studied 22 healthy adult men and women: 12 young (18–28 yr; 7 men, 5 women) and 10 older (55–67 yr; 6 men, 4 women). All subjects were healthy, as assessed by medical history and fasting lipid profiles. In addition, older subjects underwent a physical examination with resting ECG and ultrasound echocardiography (Toshiba Powervision 6000, Tochigi, Japan), as well as ECG and blood pressure assessments during graded treadmill exercise to exhaustion. Subjects were nonsmokers and were not regularly taking any medications or vitamin supplements. The nature, purpose, and risks of the study were explained to each subject before written, informed consent was obtained. The experimental protocol was approved by the Human Research Committee at the University of Colorado at Boulder and was performed in the Boulder Satellite General Clinical Research Center.

**Experimental procedures.** Following successful completion of all screening visits, subjects reported to the General Clinical Research Center on four separate occasions. During the first visit, subjects were habituated to the procedures undertaken for determination of Q\(\text{max}\) and V\(\text{O}_2\) max. After a brief warm-up, subjects performed incremental treadmill exercise until volitional exhaustion. Subjects then performed constant-load treadmill exercise twice at the same speed and grade accomplished at the end of the incremental exercise, until volitional exhaustion. Exercise bouts were separated with brief (~2 min) rest periods. V\(\text{O}_2\) was determined continuously throughout the incremental treadmill exercise, and Q\(\text{max}\) was determined at the point of exhaustion of the incremental and constant-load treadmill exercise bouts. The same procedures were used to determine V\(\text{O}_2\) max and Q\(\text{max}\) during the remaining three visits. Before treadmill exercise during the second period. V\(\text{O}_2\) was determined continuously throughout the incremental treadmill exercise, and Q\(\text{max}\) was determined at the point of exhaustion of the incremental and constant-load treadmill exercise bouts. The same procedures were used to determine V\(\text{O}_2\) max and Q\(\text{max}\) during the remaining three visits. Before treadmill exercise during the second...
and third visits, subjects received either 1) intravenous ascorbic acid administration [American Regent Laboratories; priming bolus of 0.06 g/kg fat-free mass dissolved in 100 ml of saline, infused at 5 ml/min (20-min infusion) and “drip infusion” of 0.02 g/kg fat-free mass dissolved in 30 ml of saline administered over 20 min at 1.5 ml/min]; or 2) saline infusion at the same rates. The order of infusions was randomized, and ascorbic acid was administered in a double-blind fashion. During the 30 days before the final visit, all subjects ingested 500 mg/day of ascorbic acid (time-release capsules, Goldline Laboratories, Miami, FL). The rationale for these doses and methods of administration has been described previously (2, 11, 12), and the acute dose has been shown to reduce oxidative stress in both young and older adults (2) and restore flow-mediated dilatation in sedentary older men (12). Blood was sampled at three time points for determination of plasma concentration of ascorbic acid and oxidized low-density lipoproteins, a systemic marker of oxidative stress (36); before and following the intravenous ascorbic acid administration, and following the 30-day oral administration.

**Experimental measures.** \( V_{\text{O}_2\text{max}} \) was determined via indirect calorimetry (Medgraphics CardiO2CP, St. Paul, MN). \( Q_{\text{max}} \) was determined via open-circuit acetylene breathing, as previously described (3, 21). After a 6- to 10-min warm-up period, each subject ran or walked at a comfortable speed that corresponded to 70–80% of age-predicted maximal heart rate. Treadmill grade was increased 2.5% every 2 min until volitional exhaustion. At the end of each stage, subjects were asked to rate their perception of effort by using a Borg scale (6–20 scale). Each incremental treadmill test lasted between 8 and 12 min. Maximal heart rate was defined as the highest value recorded from ECG recordings during the test. To ensure that each subject attained \( V_{\text{O}_2\text{max}} \), at least three of the following four criteria were met by each subject: 1) a plateau in \( V_{\text{O}_2} \) with increasing exercise intensity, 2) a respiratory exchange ratio of at least 1.15, 3) an achievement of the age-predicted maximal heart rate (±10 beats/min), and 4) a rating of perceived exertion of at least 18 units (5). Through-out the brief rest periods before the constant-load treadmill exercise, subjects walked at a comfortable speed at 0% gradient and were allowed to consume water ad libitum. During constant-load exercise, the speed and gradient were rapidly increased until both were equivalent to that accomplished at the end of the incremental exercise test (target workload achieved in ~2 min). Subjects maintained this workload until volitional exhaustion, whereupon \( Q_{\text{max}} \) was determined. \( Q_{\text{max}} \) data were only considered for analysis if the heart rate at the 30-day oral administration.

### Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>7/5</td>
<td>6/4</td>
</tr>
<tr>
<td>Age, yr</td>
<td>23±1</td>
<td>61±1*</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>72±3</td>
<td>77±5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24±1</td>
<td>26±1</td>
</tr>
<tr>
<td>%Body fat</td>
<td>27±3</td>
<td>31±2</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>49±3</td>
<td>51±3</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>4.1±0.2</td>
<td>5.4±0.2*</td>
</tr>
<tr>
<td>High-density lipoprotein, mmol/l</td>
<td>1.2±0.1</td>
<td>1.3±0.1</td>
</tr>
<tr>
<td>Low-density lipoprotein, mmol/l</td>
<td>2.4±0.1</td>
<td>3.6±0.2*</td>
</tr>
<tr>
<td>Triglyceride, mmol/l</td>
<td>1.0±0.1</td>
<td>1.1±0.1</td>
</tr>
<tr>
<td>Resting heart rate, beats/min</td>
<td>68±4</td>
<td>86±3</td>
</tr>
<tr>
<td>Resting blood pressure, mmHg</td>
<td>114/72±2/4</td>
<td>123/79±5/2*</td>
</tr>
<tr>
<td>Left ventricular chamber diameter, mm</td>
<td>46.0±1.4</td>
<td>48.6±2.2</td>
</tr>
<tr>
<td>Left ventricular volume at diastole, ml</td>
<td>61.6±4.2</td>
<td>76.2±6.6</td>
</tr>
<tr>
<td>Early-to-late ventricular filling ratio</td>
<td>2.1±0.2</td>
<td>1.2±0.1*</td>
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<tr>
<td>Isovolumetric relaxation time, ms</td>
<td>62.8±4.8</td>
<td>78.7±4.5*</td>
</tr>
</tbody>
</table>

*Values are means ± SE. *P < 0.05 compared with young adults.

### Table 2. Habitual daily dietary intake

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy intake, kJ/day</strong></td>
<td>10,538±582</td>
<td>8,265±783*</td>
</tr>
<tr>
<td><strong>Carbohydrates, g</strong></td>
<td>323±23</td>
<td>250±24*</td>
</tr>
<tr>
<td><strong>Fat, g</strong></td>
<td>99±6</td>
<td>75±10*</td>
</tr>
<tr>
<td><strong>Protein, g</strong></td>
<td>84±5</td>
<td>80±8</td>
</tr>
<tr>
<td><strong>Vitamin C, mg</strong></td>
<td>129±20</td>
<td>146±14</td>
</tr>
<tr>
<td><strong>Vitamin E, IU</strong></td>
<td>10±1</td>
<td>12±2</td>
</tr>
</tbody>
</table>

*Values are means ± SE. *P < 0.05 compared with young adults.

Dietary intake of antioxidants (vitamins C and E), together with macro- and micronutrients, were estimated from food diaries maintained for 4 consecutive days (3 weekdays and 1 weekend day). Subjects kept accurate and complete diet records and were provided with a diet scale (Scalesman, Target, Minneapolis, MN) to weigh all food. A registered dietitian subsequently analyzed all of the food diaries using standard computer-assisted procedures (ESHA-The Food Processor, version 7.6, Salem, OR).

Fat mass and fat-free mass were measured using dual-energy X-ray absorptiometry (DXA-IQ; Lunar Radiation, Madison, WI, software version 4.1).

### Statistical analysis. Two-way ANOVA with repeated measures on one factor was used to examine differences in dependent variables between the groups following saline (control) and (acute and chronic) administration of ascorbic acid. Multiple comparisons of factor means were performed by using the Newman-Keuls test. Two-way ANOVA was also used to compare plasma concentration of ascorbic acid and markers of oxidative stress between young and older adults across time. The relation between \( Q_{\text{max}} \) and \( V_{\text{O}_2\text{max}} \) was determined by simple correlation analysis. The level of statistical significance was set at \( P < 0.05 \). Data are expressed as means ± SE.

### RESULTS

Selected subject characteristics are presented in Table 1. Compared with the young, the older adults had greater diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, and isovolumetric relaxation time, and lower early-to-late ventricular filling ratio (\( P < 0.05 \)). Mean daily dietary intake is presented in Table 2. Dietary intake of vitamins C and E did not differ between young and older adults (\( P > 0.05 \)).

Plasma concentration of ascorbic acid at baseline and following the acute and chronic administrations is presented in Fig. 1. There were no differences between the young and older adults at any time. Plasma concentration increased in all subjects following the acute but not chronic administration, establishing that we were able to increase plasma concentration of ascorbic acid to supraphysiological levels in both young and older adults with acute administration. Oxidized low-density lipoprotein concentration was negatively associated with maximum heart rate (\( r = -0.49, P = 0.02 \)) and was greater (\( P < 0.001 \)) in the older (57 ± 5 U/l) compared with the young (34 ± 3 U/l) adults and was reduced (\( P < 0.02 \)) in both groups following acute (~6 ± 2%) but not chronic (\( P = 0.18 \)) ascorbic acid administration, establishing that we were able to reduce oxidative stress in both groups with acute administration (Fig. 2).

Values for control (baseline) \( V_{\text{O}_2\text{max}} \) and \( Q_{\text{max}} \) were positively related [\( r = 0.76, P < 0.001 \); \( V_{\text{O}_2\text{max}} = (0.16 \times Q_{\text{max}}) + 0.01 \)] and were lower (\( P < 0.05 \)) in the older (34 ± 2 ml·kg⁻¹·min⁻¹ and 16.1 ± 1.1 l/min) compared with the young (43 ± 3 ml·kg⁻¹·min⁻¹ and 20.2 ± 0.9 l/min, respec-
tively) adults ($P < 0.01$). Following ascorbic acid administration, neither $V\dot{O}_2\max$ (Fig. 3) nor $Q\dot{max}$ (Fig. 4) was changed ($P > 0.05$). Similarly, maximal heart rate was lower ($P < 0.001$) in the older (166 ± 2 beats/min) compared with the young (194 ± 2 beats/min) adults and was unchanged ($P = 0.41$) with ascorbic acid administration (young acute 195 ± 2; young chronic 194 ± 2; older acute 166 ± 4; older chronic 167 ± 4 beats/min). Finally, maximum stroke volume was similar ($P > 0.05$) in the older (97 ± 7 ml) compared with the young (104 ± 5 ml) adults and was unchanged ($P > 0.05$) with ascorbic acid administration (young acute 104 ± 6; young chronic 99 ± 4; older acute 98 ± 7; older chronic 100 ± 8 ml).

Irrespective of age, $V\dot{O}_2\max$, $Q\dot{max}$, and stroke volume were greater in men compared with women ($P < 0.002$); however, there were no sex-differences or age-sex interactions ($P > 0.05$) pertaining to the response of any of these variables to administration of ascorbic acid.

DISCUSSION

In the present study, we reasoned that, because oxidative stress typically increases with age even in healthy adults (19, 24, 25, 29, 33), and can impair cardiac β-adrenergic-receptor responsiveness (27) and is negatively associated with left ventricular ejection fraction (40), it might contribute to the reduction in $Q\dot{max}$ and $V\dot{O}_2\max$, with primary adult aging. Our results, however, do not support this hypothesis.

Based on three lines of evidence, we are confident that we were able to reduce oxidative stress, with our acute administration of ascorbic acid: 1) plasma concentration of oxidized low-density lipoprotein, a systemic marker of oxidative stress, was significantly reduced; 2) the same dosing regimen has been shown previously to reduce oxidative stress (plasma isoprostane concentration) in a similar study population (2); and 3) the same dosing regimen reverses oxidative stress-mediated reductions in other physiological functions in older sedentary humans, including cardiovascual baroreflex sensitivity (31) and brachial artery flow-mediated dilation (12).

The influence of antioxidant administration on exercise performance has been studied previously, often without a hypothesized mechanism linking oxidative stress to performance (41), resulting in conflicting results (6, 16, 20, 23, 28). To explain these apparent discrepancies, some authors have suggested that antioxidant administration may only prove to be beneficial for populations with elevated baseline oxidative stress (6, 41) (or low-endogenous antioxidant levels) such as vascular disease patients (18), smokers (37), or older adults (12, 31). In the present study, there was no age-associated effect of acute or chronic ascorbic acid administration on...
VO₂max or Qmax, despite elevated baseline oxidative stress in the older adults.

Our study combined men and women in both the young and older age groups. There is some evidence to suggest that men and women may utilize different mechanisms to augment cardiac output during maximal exercise (13). While we were able to report greater VO₂max, Qmax, and stroke volume in men, irrespective of age, we found no evidence of sex differences or age-sex interactions pertaining to any of these variables in response to administration of ascorbic acid.

Our acute intravenous administration of ascorbic acid had no effect on VO₂max or Qmax in either young or older adults. It may be that oxidative stress impairs VO₂max and Qmax in a genomic-mediated manner, such as damage to DNA, and thus a more prolonged program of ascorbic acid administration is required to improve aerobic capacity. However, a 30-day oral supplementation (500 mg/day) of ascorbic acid also failed to impact VO₂max or Qmax. On the other hand, the lack of effect with the 30-day oral administration is hardly surprising given the absence of an effect of supraphysiological doses of ascorbic acid on VO₂max or Qmax (acute infusions). Except for the initial 2 h after daily administration, plasma concentrations of ascorbic acid are much lower during long-term oral supplementation than those achieved with acute intravenous infusion (8, 10, 12), presumably reflecting attenuated ability to reduce oxidative stress. These observations indicate that 30 days of moderate daily ascorbic acid supplementation have no obvious therapeutic efficacy for attenuating the age-associated decline in VO₂max or Qmax in older adults.

There are several other possible explanations of our data. Ascorbic acid administration may indeed have restored β-adrenergic-receptor responsiveness, however, not to a degree sufficient to increase Qmax and VO₂max. Alternatively, ascorbic acid administration may have had no effect on β-adrenergic-receptor responsiveness, and thus Qmax and VO₂max were unchanged. A direct determination of cardiac β-adrenergic-receptor responsiveness would have definitively addressed this issue; the nonexistence of this determination represents a clear limitation to our study. Additionally, maximal stroke volume was not different between young and older adults, an observation that is supported by previous reports (13, 26). It may be that, in our sample of older adults, myocardial contractility was not reduced, and the decrease in Qmax was mediated primarily by a decrease in maximal heart rate.

Another potential limitation of our study pertains to the effectiveness of an acute intravenous and/or chronic oral administration of ascorbic acid on alleviating oxidative stress within the heart. Although decreased plasma oxidized low-density lipoprotein concentration may be reflective of reduced oxidative stress in tissues primarily responsible for producing these compounds, we have no direct evidence that oxidative stress was reduced within the contractile tissues of the heart. In a previous study, showing augmented β-adrenergic-receptor-mediated myocardial contractility with ascorbic acid administration (27), the ascorbic acid was delivered directly into the heart (via cardiac catheterization), as opposed to intravenous administration as in the present study. The proximity of administration to the target tissue may contribute to differences in the effects of ascorbic acid between these studies.

Additionally, it is possible that, although acute ascorbic acid administration increased plasma concentration to supraphysiological levels and reduced baseline oxidative stress, it may have failed to attenuate increases in exercise-induced oxidative stress; thus, at exhaustion, elevated oxidative stress may still have limited Qmax. This idea is in keeping with previous data that have demonstrated significant oxidative stress in young healthy adult men following vigorous exercise, despite decreased baseline oxidative stress with antioxidant administration (22). We did not determine oxidative stress postexercise in the present study; however, given the relatively large quantity of ascorbic acid administered, it is likely that, at exhaustion, the circulating concentration of ascorbic acid was probably still very high, and thus exogenous antioxidant activity may also have remained high.

We chose to use ascorbic because it is one of the most potent water-soluble antioxidants in humans. Ascorbic acid administration results in the scavenging of many ROS, including those produced by lipid peroxidation (14), and is a well-established antioxidant model for reducing ROS/oxidative stress in human cardiovascular research. That being said, we cannot exclude the possibility that other antioxidants (e.g., allopurinol, vitamin E, glutathione, β-carotene, and/or superoxide dismutase) may have produced improvements in Qmax and VO₂max. Present experimental findings, however, are mixed regarding the effect of vitamin E (and, even more so, β-carotene) on cardiovascular function (7, 9, 15). Even combinations of antioxidants (normally ascorbic acid, vitamin E, and β-carotenes), when given orally at physiological doses, show conflicting results on cardiovascular outcomes (17, 30).

In summary, the results of the present study indicate that the age-associated decline in VO₂max and Qmax is unaffected by acute or chronic (30 days) administration of moderate daily ascorbic acid (vitamin C) supplementation.

ACKNOWLEDGMENTS

We thank Benjamin L. Garvey for technical and administrative assistance.

GRANTS

This study was supported by National Institutes of Health Grants AG-06537, AG-13038, AG-15897, AG-022053, and RR-00051.

REFERENCES


