Ascorbate infusion increases skeletal muscle fatigue resistance in patients with chronic obstructive pulmonary disease

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1Geriatric Research, Education, and Clinical Center, George E. Whalen Veterans Affairs Medical Center, Salt Lake City, Utah; 2Department of Exercise and Sport Science, University of Utah, Salt Lake City, Utah; and 3Department of Internal Medicine, Division of Geriatrics, University of Utah, Salt Lake City, Utah

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ROSMAN MJ, GARTEN RS, GROOT HJ, VAN REESE, ZHAO J, AMANN M, RICHARDSON RS. Ascorbate infusion increases skeletal muscle fatigue resistance in patients with chronic obstructive pulmonary disease. Am J Physiol Regul Integr Comp Physiol 305: R1163–R1170, 2013. First published September 25, 2013; doi:10.1152/ajpregu.00360.2013.—Chronic obstructive pulmonary disease (COPD) is associated with systemic oxidative stress and skeletal muscle dysfunction. The purpose of this study was to examine the impact of intravenous ascorbate administration (AO) on biological markers of antioxidant capacity and oxidative stress, and subsequently skeletal muscle function during dynamic, small muscle mass exercise in patients with COPD. Ten patients with spirometric evidence of COPD performed single-leg knee extensor (KE) trials matched for intensity and time (isotime) following intravenous ascorbate (2 g) or saline infusion (PL). Quadriceps fatigue was quantified by changes in force elicited by maximal voluntary contraction (MVC) and magnetic femoral nerve stimulation (Qw,pot). AO administration significantly increased antioxidant capacity, as measured by the ferric-reducing ability of plasma (PL: 1 ± 0.1 vs. AO: 5 ± 0.2 mM), and significantly reduced malondialdehyde levels (PL: 1.16 ± 0.1 vs. AO: 0.97 ± 0.1 nmol). Additionally, resting blood pressure was significantly reduced (PL: 104 ± 4 vs. AO: 93 ± 6 mmHg) and resting femoral vascular conductance was significantly elevated after AO (PL: 2.4 ± 0.2 vs. AO: 3.6 ± 0.4 ml/min·mmHg−1). During isotime exercise, the AO significantly attenuated both the ventilatory and metabolic responses, and patients accumulated significantly less peripheral quadriceps fatigue, as illustrated by less of a fall in MVC (PL: −11 ± 2% vs. AO: −5 ± 1%) and Qw,pot (PL: −37 ± 1% vs. AO: −30 ± 2%). These data demonstrate a beneficial role of AO administration on skeletal muscle fatigue in patients with COPD and further implicate systemic oxidative stress as a causative factor in the skeletal muscle dysfunction observed in this population.

Likely due to free radical scavenging, the infusion of supraphysiologic doses of the antioxidant ascorbate (AO) have previously been documented to restore vascular function in several pathophysiological conditions such as heart failure (19), hypertension (36), diabetes (38), as well in chronic smokers (18). In addition, high-dose AO infusion has been documented to improve resting (20) and exercising (14, 23) skeletal muscle blood flow in healthy older individuals. Improving limb blood flow, and possibly oxygen delivery, has the potential to attenuate the rate of development of peripheral muscle fatigue (3). Interestingly, intravenous AO administration also ameliorated the exaggerated exercise pressor reflex during plantar flexion exercise in patients with peripheral artery disease, which was attributed to a reduction in excessive group III/IV afferent stimulation under basal conditions (27). Decreasing the group III/IV afferent signal from the lower limbs has also been documented to extend exercise time to exhaustion in patients with COPD (17). Therefore, free radical scavenging by AO may confer beneficial vascular effects and dampen group III/IV afferent signaling, potentially translating into fatigue resistance in patients with COPD.

Thus the purpose of this study was to examine the impact of intravenous AO administration, a potent water-soluble antioxidant with no known side effects, on oxidative stress and skeletal muscle fatigue during dynamic KE exercise in patients with COPD. In addition, this study sought to comprehensively evaluate the impact of reducing oxidative stress with AO on the physiological responses to KE exercise in patients with COPD.

SKELETAL MUSCLE DYSFUNCTION plays a prominent role in limiting exercise and activities of daily living in patients with chronic obstructive pulmonary disease (COPD) (21, 22). Numerous factors, including inactivity and skeletal muscle de-training (34), mitochondrial dysfunction (9), and oxidative stress (30) have all been implicated in the skeletal muscle dysfunction associated with COPD. Of these factors, the contribution of oxidative stress to reduced exercise capacity in patients with COPD has been well documented (11, 13, 24). Specifically, previous research has demonstrated an inverse correlation between exercise time to exhaustion and evidence of lipid peroxidation (12), as well as the favorable effects of preexercise antioxidant pretreatment with N-acetylcysteine (24) on performance in patients with COPD. Therefore, in patients with COPD, exercising skeletal muscle is a significant source of oxidative stress, the magnitude of oxidative stress likely impairs skeletal muscle function, and the modulation of redox state may enhance exercise capacity in this population.

Accordingly, our group previously utilized an acute, readily available, oral antioxidant cocktail (vitamins C, E, and α-lipoic acid), with documented efficacy (43), to examine the impact of oxidative stress on skeletal muscle function in COPD (32). The antioxidant cocktail decreased the electron paramagnetic resonance (EPR) spectroscopy free radical signal, but did not impact skeletal muscle fatigue measured after isotime knee extensor (KE) exercise in patients with COPD. However, the individual responses to the oral antioxidant cocktail were mixed, with only half of the patients exhibiting a substantially reduced EPR spectroscopy signal. Therefore, in this prior study (32), the role of free radicals on skeletal muscle fatigue in patients with COPD was not fully elucidated.

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We tested the hypotheses that in patients with COPD intravenous AO administration would 1) improve antioxidant capacity and decrease oxidative stress and, 2) decrease the magnitude of peripheral quadriceps fatigue induced by KE exercise matched for intensity and duration (isotime).

METHODS

Subjects. Written, informed consent was obtained from all participants before their inclusion in this study, and the Institutional Review Boards of the University of Utah and the Salt Lake City Veterans Affairs Medical Center approved all protocols. Ten patients with COPD were enrolled based on spirometric evidence of moderate to severe airflow obstruction [FEV1/FVC ≤ 0.7 (10)], as assessed by standard pulmonary function tests performed during an initial visit to the laboratory. General anthropometric characteristics, including thigh volume, which was used to estimate quadriceps muscle mass (16), were also determined during this visit. Resting arterial blood analyses, collected in a parallel study in which the current subjects took part, are also presented here to better characterize the patients.

Exercise protocols and general procedures. All subjects were familiarized with single-leg KE exercise, which was performed at a cadence of 60 rpm, during two preliminary visits to the laboratory. Subsequently, peak KE work rate was determined with subject-specific protocols designed to reach exhaustion within 8–12 min, consisting of 2–5 W/min increases. The experimental protocol is depicted in Fig. 1. After the peak work rate tests, subjects performed at least two practice constant-load exercise trials at 80% of maximal workload to the limit of tolerance to determine a target exercise intensity and duration for the subsequent isotime trials. The intensity of the practice trials was adjusted until subjects could maintain the intensity, at a cadence of 60 rpm, for ~6 to 8 min before their cadence dropped below 50 rpm and the trial was terminated. Once these criteria were met, the trial time was adopted as the target time for the subsequent isotime trials. Next, in a repeated-measures design, isotime trials, separated by 48–96 h, were performed following either a bolus infusion of AO (100 mg/ml AO dissolved in normal saline, infused at 1 ml/min for 20 min) or saline (PL: 0.9% NaCl infused at 1 ml/min for 20 min) via an intravenous catheter in the arm (Fig. 1).

The patient and all members of the research team, except for the individual administering the AO or PL, were blinded to the experimental condition.

Neuromuscular function tests were performed before infusion, after infusion (but before exercise), and 10 min after the isotime trials. In addition, venous blood samples were taken before and immediately after the isotime trials to determine pro- and antioxidant status, and for spin trapping and EPR spectroscopy to directly assess free radical concentration. Before each exercise bout, 1 min of resting data were collected and subjects performed 1 min of unloaded warmup KE exercise. Ventilation, gas exchange, heart rate (HR), mean arterial pressure (MAP), ratings of perceived exertion and breathlessness, arterial oxygen saturation, femoral blood flow, and quadriceps electromyograms (EMG) were measured during the isotime trials.

Oxidative stress, antioxidant assays, and direct measurement of free radicals. Plasma samples were stored at −80°C until analysis. Lipid peroxidation, a marker of oxidant damage, was assessed by plasma malondialdehyde levels (Bioxytech LPO-586, Foster City, CA). Total antioxidant capacity was evaluated by determining the ferric-reducing ability of plasma (FRAP), using the method described by Benzie and Strain (6). The efficacy of the AO specific to plasma ascorbate levels was assayed as previously described (8) (CosmoBio, Carlsbad, CA). Free radical scavenging, assessed by superoxide dismutase and catalase activity, was also assayed in the plasma (42) (Cayman Chemical, Ann Arbor, MI). EPR spectroscopy was performed on pre- and postexercise blood samples to directly assess the ability of the AO to reduce the concentration of free radicals with an EMX X-band spectrometer (Bruker, MA), as previously described (31, 32).

Pulmonary and cardiovascular responses. Ventilation and pulmonary gas exchange were measured at rest and during exercise using an open-circuit system (ParvoMedics, Sandy, UT). HR, determined from the R-R interval of a three-lead electrocardiogram, and arterial oxygen saturation (SaO2), estimated using a pulse oximeter (Nellcor N-595, Pleasanton, CA) with adhesive forehead sensors, were also acquired during these trials at 200 Hz using a data acquisition system (AcqKnowledge; Biopac Systems, Goleta, CA). MAP was determined with a finometer (Finapres Medical Systems, The Netherlands) at heart level. Patients were asked how hard their leg was working (rating of perceived exertion, RPE) and how labored was their breathing.

Ascorbate
Isotime:
Placebo
Trial (n = 4)

Ascorbate
Isotime:
Placebo
Trial (n = 6)

Isotime:
Ascorbate
Trial (n = 4)

Isotime:
Ascorbate
Trial (n = 6)

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Fig. 1. Study protocol schematic. MVC, maximal voluntary contraction. Qtw,pot, potentiated twitch force.
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Fatigue and oxidative stress in COPD

Leg blood flow. Measurements of femoral artery blood velocity and vessel diameter in the leg being studied were performed at rest and throughout isotonic exercise, using a Logiq 7 ultrasound system (General Electric Medical Systems) as previously described (39). Blood flow in the femoral artery was calculated as the following: blood flow = (mean velocity)π(arterial diameter/2)² × 60.

Quadriceps electromyograms. Quadriceps EMGs were recorded from the vastus lateralis muscle during exercise from electrodes placed in a bipolar configuration with an interelectrode distance of 20 mm over the middle of the muscle belly, with the active electrodes placed over the motor point of the muscle and the reference electrode in an electrically neutral site (4). To ensure similar electrode placement between trials, the electrode location was marked with indelible ink. Raw EMG signals were filtered with a bandpass filter (with a low-pass cut-off frequency of 15 Hz and a high-pass cut-off frequency of 650 Hz) and after visual inspection of the filtered signal; a threshold voltage was set to identify the onset of EMG activity (AcqKnowledge; Biopac Systems). For data analysis, the integral of each EMG burst voltage was set to identify the onset of EMG activity (AcqKnowledge; Biopac Systems). For data analysis, the integral of each EMG burst activity was set to identify the onset of EMG activity (AcqKnowledge; Biopac Systems). Raw EMG signals were filtered with a bandpass filter (with a low-pass cut-off frequency of 15 Hz and a high-pass cut-off frequency of 650 Hz) and after visual inspection of the filtered signal; a threshold voltage was set to identify the onset of EMG activity (AcqKnowledge; Biopac Systems).

Neuromuscular function assessment. The magnitude of peripheral quadriceps fatigue was quantified by pre- to postinfusion, and pre- to postexercise changes in quadriceps maximal voluntary contraction (MVC) and Qtw,pot evoked by supramaximal magnetic stimulation of the femoral nerve (4, 29) with a magnetic stimulator (Magstim 200, The Magstim, Wales, UK) connected to a double 70-mm coil (26). Specifically, while laying semirecumbent with a knee joint angle of 90°, patients refrained from the use of tobacco products for 12 h before all data collection. Two patients qualified for supplemental oxygen therapy; these patients, however, at the time of data collection, reported any side effects of AO or PL administration and were therefore successfully blinded to the experimental conditions. Supramaximality of magnetic nerve stimulation was demonstrated in all patients by evidence of a plateau in evoked force with increasing stimulus intensity.

Antioxidant efficacy. Before exercise, AO caused an ∼10-fold elevation in plasma ascorbate levels (Fig. 2A). AO infusion also increased endogenous antioxidant capacity, as measured by FRAP, and resulted in greater free radical scavenging, as evidenced by increased superoxide dismutase enzymatic catalase activities (Fig. 2, B–D). Consequently, resting malondialdehyde levels, a marker of lipid peroxidation and oxidative stress, were decreased following AO infusion (Fig. 2E). In contrast, and somewhat surprisingly, there was no detectable difference in plasma free radical levels, directly measured by EPR spectroscopy, between conditions (AO: 10.9 ± 3.1 AU vs. PL: 11.6 ± 3.7 AU, P > 0.05).

After exercise, AO and FRAP remained elevated over PL values in the AO condition (AO: 107.6 ± 8.1 µg/ml vs. 12.9 µg/ml, P < 0.05; FRAP: 1.5 ± 0.08 mM vs. PL: 0.97 ± 0.08, P < 0.05 exercise, for AO and PL, respectively). In addition, MDA was decreased to a similar extent as before exercise (AO: 0.94 ± 0.1 µM vs. PL: 1.2 ± 0.1 µM, P < 0.05). Postexercise, there were no differences between conditions in terms of antioxidant enzyme (superoxide dismutase or catalase) activity or plasma free radical levels, assessed by EPR spectroscopy.

Isotonic trials. Acutely, MVC and Qtw,pot were unaffected by AO infusion (MVC: 374 ± 52 N to 374 ± 53 N, P > 0.05; Qtw,pot: 105 ± 13 N to 103 ± 13 N, P > 0.05, for pre- and postinfusion, respectively), and these values were not different from the pre- and post-PL infusion values. At baseline, before exercise, MAP was reduced following the AO infusion (Fig. 3). Despite the decrease in perfusion pressure, femoral artery blood flow was not different between conditions (P > 0.1), and thus femoral vascular conductance was significantly elevated in the AO condition (Fig. 3). Because of movement artifact, differences in MAP could not be evaluated throughout the exercise trials using Borg’s CR10 scale (7).

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (Mean ± SD)</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>62 ± 3</td>
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<tr>
<td>Height, m</td>
<td>1.7 ± 0.03</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84 ± 7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28 ± 2</td>
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<tr>
<td>Quadriceps muscle mass, kg</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>Peak knee-extension work rate, W</td>
<td>28 ± 3</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7/3</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td></td>
</tr>
<tr>
<td>FVC, l (% predicted)</td>
<td>3.6 ± 0.2 (86 ± 5)</td>
</tr>
<tr>
<td>FEV1 in 1 s, l/s (% predicted)</td>
<td>1.8 ± 0.2 (57 ± 5)</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>51 ± 5</td>
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<tr>
<td>Resting arterial blood gases</td>
<td></td>
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<tr>
<td>Hemoglobin concent. g/dl</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>Oxyhemoglobin, %</td>
<td>92 ± 1</td>
</tr>
<tr>
<td>Partial pressure of oxygen, mmHg</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>Partial pressure of carbon dioxide, mmHg</td>
<td>32 ± 2</td>
</tr>
<tr>
<td>Bloodflow in femoral artery</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.45 ± 0.01</td>
</tr>
</tbody>
</table>

Values expressed as means ± SE. FEV1/FVC, forced expiratory volume in 1 s relative to forced vital capacity; BMI, body mass index.

RESULTS

Subject characteristics. Subject characteristics are documented in Table 1. One patient was a current smoker, who refrained from the use of tobacco products for 12 h before all data collection. Two patients qualified for supplemental oxygen therapy; these patients, however, at the time of data collection, reported any side effects of AO or PL administration and were therefore successfully blinded to the experimental conditions.

Statistical analysis. Two-way repeated measures ANOVA were used to compare the effect of antioxidant treatment on physiological parameters during exercise, with a Tukey post hoc analysis if a significant main effect was found. Student’s paired t-tests were used to compare the effect of AO in terms of antioxidant efficacy and indices of peripheral fatigue. Statistical significance was set at α = 0.05 for all tests. All group data are expressed as means ± SE.

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The cardiorespiratory responses to the isotime trials are depicted in Fig. 4. As illustrated, oxygen consumption (VO₂) and carbon dioxide production (VCO₂) were reduced during exercise following AO infusion at isotime minute 4, but reached similar levels at the end of exercise. In addition, ventilation rate (VE) and the ventilation relative to carbon dioxide production (VE/VCO₂) ratio were reduced in the AO condition during exercise and at the end of the isotime trials. Arterial oxygen saturation and femoral artery blood flow were not different between conditions.

With respect to the development of peripheral fatigue during exercise, the percent increase in the integrated EMG signal (Fig. 4) was reduced during exercise in the AO condition and tended to be lower at end exercise (P = 0.09). Subjects’ ratings of perceived exertion were also lower during exercise following AO infusion, as well as at the end of exercise. In line with these observations, the patients’ dyspnea ratings were reduced at the end of the isotime trials in the AO condition (6.3 ± 1 vs. 4.8 ± 1, P > 0.05, for PL and AO, respectively). There were no changes in m-wave area (PL: 80 ± 9 mVms vs. 72 ± 10 mVms).
mVms, $P > 0.05$; AO 85 ± 11 mVms vs. 82 ± 11 mVms, $P > 0.05$) or peak-to-peak-amplitude (PL: 8.7 ± 0.8 mV vs. 8.1 ± 0.9 mV, $P > 0.05$; AO 9.3 ± 1.2 mV vs. 8.8 ± 1.2 mV, $P > 0.05$) in either condition from pre- to postexercise, and these values were not different between PL and AO trials. Voluntary activation was reduced following exercise to a similar extent in both conditions (AO: −3.1 ± 0.7% vs. PL: −3.5 ± 1.6%, $P > 0.05$). Additionally, the pre- to postexercise changes in MVC and $Q_{\text{tw}, \text{pot}}$ were reduced to a lesser extent in the AO condition, suggestive of less peripheral quadriceps fatigue (Fig. 5).

**DISCUSSION**

This study sought to evaluate the impact of intravenous AO on systemic antioxidant capacity and oxidative stress in patients with COPD and subsequently determine the effects of...
this intervention on skeletal muscle fatigue following exercise in this population. Before exercise, AO increased antioxidant capacity and reduced oxidative stress, and these changes in the pro- and antioxidant balance were accompanied by a reduction in MAP and an increase in femoral artery vascular conductance. Exercise after AO administration, matched for time with the PL trial, was associated with attenuated ventilatory and metabolic responses to the work and a slowed rate of fatigue development (rise in quadriceps iEMG). Thus the exercise bout ultimately resulted in less of a decrease in quadriceps MVC and evoked twitch force following exercise, revealing improved fatigue resistance during exercise. Collectively, these data demonstrate a beneficial effect of intravenous AO administration on systemic oxidative stress and skeletal muscle function in patients with COPD. Moreover, these data further implicate oxidative stress as a factor contributing to skeletal muscle dysfunction in COPD.

Oxidative stress and fatigue. Previously, dynamic KE exercise has been documented to increase markers of oxidative damage in patients with COPD, but not in healthy control subjects (11, 12). In this prior study, within the patient group, the magnitude of increase in oxidative stress was negatively correlated with exercise time to exhaustion (12). Furthermore, when patients with COPD were pretreated with the pharmacological antioxidant N-acetylcysteine before performing KE exercise, markers of oxidative damage were reduced and exercise time to exhaustion was improved (24). Excessive elevations in free radicals, within muscle itself, have been suggested to impair function by decreasing the calcium sensitivity of the myofilaments and attenuating calcium reuptake by the sarcoplasmic reticulum, among other mechanisms (1). Collectively, these studies suggest that oxidative stress contributes to skeletal muscle dysfunction in patients with COPD, and decreasing the oxidant load has the potential to improve the intramuscular redox state and therefore skeletal muscle function in this population.

In the current study, intravenous AO decreased plasma markers of oxidative damage, improved the antioxidant status (Fig. 2), and attenuated exercise-induced fatigue (Fig. 5) in patients with COPD. Consequently, these data reveal that KE exercise performed by patients with COPD for the same duration and at the same intensity with AO infusion is associated with less peripheral quadriceps fatigue than without AO infusion. Specifically, the rate of increase in the integrated EMG signal from the vastus lateralis, an index of peripheral fatigue development during exercise, was attenuated (Fig. 4), and the magnitude of decrease in quadriceps MVC and Q\text{tw,pot} were diminished by ~50% and ~20%, respectively (Fig. 5). These data contrast with the lack of effect observed previously by our group following oral antioxidant administration in this population (32). However, the plasma concentration of ascorbate achieved in the current study, and consequently antioxidant capacity as assessed by FRAP, were elevated by approximately fivefold over the values obtained in the previous investigation (32), which may have enhanced the ability of the ascorbate to enter the muscle and exert beneficial effects on the myofilaments. It is therefore reasonable to hypothesize that the altered redox state following AO administration was translated into improved muscle function, potentially due to decreased intramuscular free radical accumulation and greater fatigue resistance during KE exercise. Thus these data suggest that oxidative stress contributes to skeletal muscle dysfunction in patients with COPD, and a reduction in oxidative stress lessens the magnitude of fatigue accumulated during high-intensity, small muscle mass exercise.

Physiological responses to exercise. Feedback from skeletal muscle group III and IV afferent fibers contribute to the cardiovascular and ventilatory response to dynamic exercise (2). In the current study, ascorbate infusion led to a reduction in V\text{E} and V\text{E}/V\text{CO}_2 ratio (Fig. 4) as well as attenuated sensations of dyspnea at the same exercise time points in the PL condition. The attenuated increase in the integrated EMG signal during exercise in the AO condition suggests less peripheral fatigue development during exercise. This is largely determined by the accumulation of metabolic by-products such as hydrogen ions and inorganic phosphates (41), as well as reactive oxygen species, within the muscle (1). These exercise-induced metabolites, as well as oxidative stress, have also been documented to activate group III and IV afferent fibers (15, 28). Thus the attenuated ventilatory responses to the exercise bouts may have been the result of improved muscle function following antioxidant administration due to an improved intramuscular redox state. This reduced metabolic perturbation during exercise would, in turn, diminish the requisite increase in V\text{O}_2 and V\text{CO}_2 during exercise in the AO condition (Fig. 4).

Alternatively, oxidative stress has been documented to directly stimulate group IV afferent fibers (15), and blocking afferent feedback with spinal anesthesia attenuated the ventilatory response to exercise in patients with COPD (17). Therefore, reducing oxidant-driven afferent activity with the AO infusion may have contributed to the reduced ventilatory response in the AO condition in the current study. Collectively, these data reveal that reducing oxidative stress by intravenous AO administration was associated with an overall attenuation in the ventilatory and metabolic responses to exercise. These, likely positive, changes may be attributed to reduced stimulation of lower limb afferent fibers potentially due to improved muscle function during exercise and decreased metabolite accumulation, or less direct stimulation of afferent fibers by oxidative stress.

Blood pressure and vascular conductance. Research regarding the hypotensive effect of antioxidant administration is equivocal. However, in a small, tightly controlled experiment, our group has previously observed a tendency for acute oral antioxidant supplementation to reduce arterial blood pressure in normotensive, older individuals (44), whereas chronic antioxidant treatment has been associated with reduced blood pressure in young healthy males (33). Under basal conditions in the current study, as is not unusual in this population (35), the patients with COPD had an average “high-normal” MAP of ~104 mmHg, and this tendency to exhibit elevated blood pressure is associated with increased cardiovascular disease risk (40). Intriguingly, intravenous AO administration resulted in an ~10- to 15-mmHg reduction in MAP, such that the average resting blood pressure for the patients with COPD in the AO condition returned to a healthy, normal value (Fig. 3). Because COPD is an independent predictor of cardiovascular disease mortality, and cardiovascular disease is a leading cause of hospitalizations in patients with mild to moderate COPD (35), ameliorating cardiovascular disease risk factors is of utmost importance. Thus these data suggest that some form of
antioxidant treatment may be important for cardiovascular disease risk management in patients with COPD.

Despite reduced arterial blood pressure with the AO, femoral artery blood flow at rest was unchanged (Fig. 3). Thus when femoral artery blood flow was normalized for the decrease in perfusion pressure, resting femoral vascular conductance was significantly elevated in the AO condition (Fig. 3). Interestingly, the magnitude of increase in femoral vascular conductance was similar to that demonstrated previously in healthy, older individuals following a similar intravenous AO infusion (20). AO has been documented to activate endothelial nitric oxide synthase (25), and coinfusion of AO and a nitric oxide synthase inhibitor negates the ability of AO to improve blood flow and vascular conductance (14). Thus, in the current study, intravenous infusion of AO may have improved nitric oxide bioavailability, perhaps by both reducing oxidative stress and promoting nitric oxide production by nitric oxide synthase, which resulted in a reduction in total peripheral resistance, leading to reduced MAP and improved femoral vascular conductance. The potential increase in nitric oxide may have also improved oxygen distribution in the working muscle and improved aerobic metabolism (37), increasing fatigue resistance during exercise. Collectively, these data support a favorable role of reducing oxidative stress on resting hemodynamic parameters in patients with COPD.

Perspectives and Significance

This study documents the ability of an intravenous AO infusion to improve antioxidant capacity and decrease oxidative stress in patients with COPD. These changes in redox balance were associated with a reduction in resting blood pressure and elevated femoral vascular conductance. In addition, dynamic KE exercise performed for the same duration and at the same intensity as the placebo condition, was associated with an attenuated rate of development of peripheral quadriiceps fatigue, improved metabolic and ventilatory responses, and less of a reduction in quadriiceps force production assessed after exercise. These data further implicate oxidative stress in the systemic, pathophysiological consequences of COPD and suggest a beneficial role for reducing oxidative stress in this population. Therefore, targeting oxidative stress with some form of antioxidant therapy in a clinical setting may represent an important therapeutic avenue for patients with COPD and suggest a beneficial role for reducing oxidative stress in patients with COPD.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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11. Couillard A, Maltais F, Saey D, Debigare R, Michaud A, Koechlin C, Delliaux S, Brerro-Saby C, Steinberg JG, Jammes Y. Plasma adenosine levels are significantly elevated in the AO condition (Fig. 3). Interest-


