Supplemental oxygen increases arterial stiffness in chronic obstructive pulmonary disease

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Summary Study objectives: Recently, we demonstrated significantly improved baroreflex sensitivity (BRS) and autonomic balance after 31% supplemental oxygen (SuppO2) in resting patients with chronic obstructive pulmonary disease (COPD). In order to investigate whether peripheral arterial stiffness changes may play a role, we evaluated changes in peripheral arterial stiffness and BRS after SuppO2.

Design: Single blinded crossover design.

Setting: Pulmonary exercise testing laboratory.

Participants: Seventy subjects with moderate to severe COPD.

Interventions: We measured arterial vascular stiffness using the augmentation index via contour analysis of the radial pulse obtained from applanation tonometry. BRS was derived using the sequence method before and after treatments with compressed air (CA) and 30% SuppO2 in 70 individuals with COPD via a counterbalanced crossover design.

Results: Paired t-tests indicated significant differences in oxygen saturation (SaO2) following SuppO2 when compared to CA (\( \bar{x} 96.0 \pm 2.0\% \) SuppO2 versus \( \bar{x} 92.6 \pm 3.6\% \) CA, \( P < 0.001 \)). BRS was significantly greater following SuppO2 compared to CA (\( \bar{x} 3.5 \pm 2.3 \text{ms/mmHg} \) SuppO2 versus \( \bar{x} 3.1 \pm 2.1 \text{CA ms/mmHg}, P < 0.03 \)). Vascular stiffness was significantly increased with SuppO2 when compared with CA (\( \bar{x} 13.3 \pm 6.1\% \) SuppO2 versus \( \bar{x} 10.8 \pm 4.9\% \) CA, \( P < 0.001 \)).

Conclusions: Our findings indicate that oxygen supplementation ameliorates BRS by changes in vasomotor activity. The amelioration of the BRS into a more normal range is a move towards the restoration of more normal physiology.
Introduction

Vascular stiffness has been shown to be sensitive to vasomotor activity changes in large and small arteries. This vasomotor activity is in part mediated via baroreflex sensitivity (BRS) and its modulation.1–5 Recently, our laboratory demonstrated, in a crossover double-blind study, that supplemental oxygen (SupO2) significantly improved BRS in resting patients with moderate and severe chronic obstructive pulmonary disease (COPD).6 A possible mechanism for this improvement could be through altered vascular stiffness. Oxygen and carbon dioxide modulate vasomotor activity in peripheral arteries via constriction and vasodilation, respectively. It is clear that oxygen supplementation can act as a vasoconstrictor in individuals with primary pulmonary hypertension, congestive heart failure and normal controls.7–10 Furthermore, evaluation of autonomic indices in these studies revealed an alteration of the baroreflex responses and heart rate variability.9–10 This relationship has not been investigated in COPD.

In order to investigate whether peripheral vascular stiffness changes following oxygen supplementation play a role in the favorable autonomic indices we had seen previously, we evaluated peripheral vascular stiffness in individuals with COPD in response to oxygen supplementation. In addition, we investigated whether changes in vascular stiffness were associated with changes in BRS in patients with COPD.

Materials and methods

Subjects

In the period from September 1999 to September 2000, 82 patients with severe COPD who were referred for exercise testing to our laboratory were screened for entry into the study. Out of those potential subjects a total of 70 patients had normal baseline electrocardiograms (ECGs) and consented to participate in this randomized double-blind crossover study. The study was carried out in the Human Performance Laboratory of the College of Physicians and Surgeons of Columbia University. The study was approved by the Institutional Review Board of the New York Presbyterian Hospital, and all subjects gave informed consent before participating. Subject demographic characteristics are presented in Table 1. Baseline arterial blood gasses and pulmonary function tests are presented in Table 2. All subjects were instructed to maintain their daily routine activity and medications throughout the entire study.

Study protocol

A multilead ECG (Marquette Medical Systems: Milwaukee, WI), and respiration via a temperature sensor (YSI reusable temperature probe: Yellow Springs, OH) placed under the subject’s nostril were recorded. Beat-to-beat radial artery blood pressures and pressure wave contours were recorded via an arterial tonometer (model 7000: Colin Medical Instruments: San Antonio, TX) attached to the subject’s wrist. Once the artery is located, the pressure transducer was placed over the vessel and depressed on the artery against underlying bone.11,12 The bone provides a contact force between the skin and the sensor approximating intra-arterial pressure (Fig. 1).12 The contact force is converted to an electrical signal by the transducer, providing a continuous beat-to-beat recording. The signal was sampled at 200 Hz/channel with an analog-to-digital (A/D) converter (DAQ-700, National Instruments, Austin, TX) and channeled into a Dell Pentium Computer. The brachial artery blood pressure was also measured

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**Table 1** Demographic profile of subjects.

<table>
<thead>
<tr>
<th>Age</th>
<th>62.8 (8.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>23.8 (3.9)</td>
</tr>
<tr>
<td>percent male</td>
<td>50%</td>
</tr>
</tbody>
</table>

All values are reported as mean (standard deviation).

**Table 2** Pulmonary parameters of included subjects.

| FEV1 | 0.78 (0.37) |
| %FEV1 | 30.4 (13.3) |
| FVC | 2.04 (0.83) |
| %FVC | 56.4 (18.8) |
| MVV | 33.0 (15.3) |
| %MVV | 31.7 (13.7) |
| Room air ABG pH | 7.42 (0.04) |
| Room air ABG pO2 | 66.4 (11.9) |
| Room air ABG pCO2 | 41.8 (8.9) |

All values are reported as mean (standard deviation). Abbreviations: FEV1—forced expiratory volume at 1 s; %FEV1—percent predicted FEV1; FVC—forced vital capacity; %FVC—percent predicted FVC; MVV—maximum voluntary ventilation; %MVV—percent predicted MVV; ABG—arterial blood gas.
with the cuff at heart level on the right arm using auscultation. Pulse oximetry was recorded using an index finger pulse oximeter (Sat-Trak Pulse Oximeter 767589-103; SensorMedics; Yorba Linda, CA). All subjects equilibrated to the environmental conditions while seated with the light dimmed for approximately 15 min. While at rest subjects were instructed to maintain breathing at 12 breaths/min and were instructed to do so through the use of a pacing light box. Control for breathing rate is recommended since breathing rate has an entrainment effect on RR interval spectra.\(^{13}\) To remove bias, a Venturi mask was placed on each patient and the patient received either 31% SuppO\(_2\) or compressed air (CA) in a random order. Randomization was based on the patient’s hospital identification number (odd number = oxygen first/CA second; even number = CA first/oxygen second). After equilibration, a 5 min data collection was performed. Then the gas mixture was switched to the alternate mixture, and after a 15 min equilibration, another 5 min of data were collected. Total test duration was approximately 40 min (two trials with equilibration on the alternative gas mixture in between).

Data acquisition

All bio-potentials were channeled through an interface board (BNC 2080, National instruments Co., Austin TX) and fed into a 12-bit A/D converter (DAQCard-700, National instruments Co., Austin TX) and then into a Pentium computer (Hitachi Vision Book Plus, San Jose, California). All data collection epochs were 5 min in duration, which is in accordance with the standards put forth by the European Task Force on Standards of Heart Rate Variability Procedures.\(^{14}\) Post acquisition data analyses were performed off-line.

Data Analysis

Baroreceptor sensitivity assessment

Baroreceptor sensitivity was derived from the 5-min epoch of collected data. The R–R intervals were delineated via a peak detection algorithm as described previously.\(^{15}\) The spontaneous BRS was determined as the slope between the change in systolic blood pressure and the change in phase of the R–R intervals by a modification of the technique of Bertinieri et al.\(^{16}\) Linear regression is performed on any episode of three consecutive beats with R–R interval lags in the same direction (either up or down), and the resultant data yield an evaluation of the BRS.\(^{15}\)

The augmentation index

The digitized pulse pressure waveform was analyzed using a customized LabView program. Specifically, an algorithm detects the waveform’s inflection point on the upstroke; this inflection is considered to signal the onset of the reflected wave.\(^{16}\) The augmentation index (AI), a noninvasive marker of vascular stiffness, was then calculated as the ratio of amplitude of the pressure wave above its systolic shoulder to the total pulse pressure.\(^{12}\) Validity and reliability of this method has been demonstrated against invasively obtained pressure signals.\(^{17}\)

Statistical analysis

Paired \(t\)-test comparisons were made between the two treatments for all dependent variables and a probability of \(P<0.05\) was considered significant.
Results

No significant differences were seen in breathing rates between the two treatments. Following oxygen supplementation ($\text{SuppO}_2$), significant differences were seen in oxygen saturation levels ($\text{SaO}_2$) when compared to CA ($\bar{x} 96.0 \pm 2.0\%$ $\text{SuppO}_2$ versus $\bar{x} 92.6 \pm 3.6\%$ CA, $P < 0.001$). BRS was significantly greater following supplemental oxygen ($\bar{x} 3.5 \pm 2.3$ ms/mmHg $\text{SuppO}_2$ versus $\bar{x} 3.1 \pm 2.1$ ms/mmHg CA) when compared to CA ($P < 0.005$) (Fig. 2).

Arterial stiffness as measured by the AI was significantly increased with $\text{SuppO}_2$ ($\bar{x} 13.3 \pm 6.1\%$ $\text{SuppO}_2$ versus $\bar{x} 10.8 \pm 4.9\%$ CA) when compared with CA ($P < 0.001$) (Fig. 3).

Discussion

The results of our investigation indicate that acute oxygen supplementation in patients with COPD significantly altered arterial vascular stiffness along with BRS at rest. Prior research has shown that patients with COPD have a reduced BRS.6,18 Furthermore, it has been suggested that the attenuation in baroreflex response was mainly due to systemic hypertension;18 however, no clear physiologic explanation for this observation has been provided. The findings of increased peripheral vascular stiffness with a corresponding increase in BRS have been documented in congestive heart failure patients.9 Additionally, increases in vascular stiffness have been seen in both obliterative pulmonary vascular disease7 and normal individuals.8,10 The findings in the current investigation suggest that $\text{SuppO}_2$ in COPD leads to an increase in arterial vascular stiffness, and this is associated with an acute enhancement of spontaneous BRS. In our subjects, there was a significant increase in the $\text{SaO}_2$ with $\text{SuppO}_2$ compared to CA. This would be in agreement with both the known vasodilator effects of mild hypoxemia and the vasoconstrictor effects of oxygen supplementation.7–10,19–22 Thus, acute $\text{SuppO}_2$ appears to result in a relative vasoconstriction with a resultant restoration of vascular tone throughout the peripheral arterial vascular tree in patients with long-standing COPD. This increase in arterial vascular tone probably results in a narrowing of the lumen of arteries which, at nearly equal blood pressure, will cause an earlier stretching and stimulation of the carotid baroreceptors. This increase in stimulation of the baroreceptors will result in a compensatory increase in vagal outflow, causing a decrease in arterial pulse pressure and heart rate along with changes in sympathetic and parasympathetic tone that our group has previously reported.6 These findings of increased parasympathetic activity in response to hyperoxia has been described in normal individuals as well.10 The overall direction of this response may be an increased parasympathetic modulation and decreased sympathetic modulation.

The clinical importance of the findings in the current investigation is in the role vascular stiffness plays in baroreflex modulation. Our findings of increased arterial vascular stiffness were seen following oxygen supplementation in moderately hypoxic individuals. Although there are several studies demonstrating an increase in peripheral vascular tone and pressure in response to hyperoxia, we are unaware of studies exploring the consequences on vascular stiffness of converting mild hypoxemia to normoxemia. The physiological benefits of the use of $\text{SuppO}_2$ in individuals with chronic hypoxemia have not been clearly elucidated, yet clear survival benefits have been documented in the long-term oxygen treatment trial and nocturnal oxygen treatment trial studies.22,23 The relationship of pulmonary hypertension and increased mortality are
established, but the mechanisms by which chronic oxygen supplementation is protective are not clear. In patients with primary pulmonary vascular obliterative disease, hyperoxia leads to decreased cardiac output, decreased stroke volume, and decreased pulmonary pressures without a change in vascular tone.\(^7\) In individuals with no fixed pulmonary hypertension, increased BRS, and the subsequent increase in parasympathetic modulation, may be important modulating factors in attenuating the progression to the development of pulmonary hypertension. Eckberg and coworkers found that mild hypoxia in which arterial \(\text{SaO}_2\) was reduced by 0.1% repeatedly lead to parasympathetic withdrawal.\(^20\) Our prior findings corroborate this by showing evidence that \(\text{SppO}_2\) augments parasympathetic tone.\(^6\) In addition to hypoxemia, COPD patients often have hypercapnia which may further exacerbate autonomic disturbances via synergistically increased sympathetic activity.\(^21\)\(^24\) Because of the possible effects of hypercapnea, the respiratory rate was controlled in the current investigation so that no differences in respiratory frequencies were seen between treatments.\(^12\) This had the effect of standardizing the effects of respiratory rate on efferent cardiac-autonomic activity.

In summary, our findings strongly suggest that oxygen supplementation acutely ameliorates BRS via changes in arterial vasomotor activity in individuals with COPD. The vasoreactivity in the peripheral arteries appears to be preserved, allowing for an improved vasomotor regulation and improvement in the BRS in response to \(\text{SppO}_2\). The clinical significance of improvement in the BRS has been shown in post-myocardial patients, where loss of BRS is a major risk factor for future cardiovascular morbidity and mortality.\(^25\) It remains to be seen whether chronic enhancement of arterial tone and BRS with \(\text{SppO}_2\) may lead to improved clinical outcomes.

Acknowledgements

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References