Effects of short-term isocapnic hyperoxia and hypoxia on cardiovascular function

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Thomson, Alastair J., Gordon B. Drummond, W. Stephen Waring, David J. Webb, and Simon R. J. Maxwell. Effects of short-term isocapnic hyperoxia and hypoxia on cardiovascular function. J Appl Physiol 101: 809–816, 2006; doi:10.1152/japplphysiol.01185.2005.—Both hypoxia and hyperoxia have major effects on cardiovascular function. However, both states affect ventilation and many previous studies have not controlled CO2 tension. We investigated whether hemodynamic effects previously attributed to modified O2 tension were still apparent under isocapnic conditions. In eight healthy men, we studied blood pressure (BP), heart rate (HR), cardiac index (CI), systemic vascular resistance index (SVRI) and arterial stiffness (augmentation index, AI) during 1 h of hyperoxia (mean end-tidal O2 79.6 ± 2.0%) or hypoxia (pulse oximeter oxygen saturation 82.6 ± 0.3%). Hyperoxia increased SVRI (18.9 ± 1.9%; P < 0.001) and reduced HR (−10.3 ± 1.0%; P < 0.001), CI (−10.3 ± 1.7%; P < 0.001), and stroke index (SI) (−7.3 ± 1.3%; P < 0.001) but had no effect on AI, whereas hypoxia reduced SVRI (−15.2 ± 1.2%; P < 0.001) and AI (−10.7 ± 1.1%; P < 0.001) and increased HR (18.2 ± 1.2%; P < 0.001), CI (20.2 ± 1.8%; P < 0.001), and pulse pressure (13.2 ± 2.3%; P = 0.02). The effects of hyperoxia on CI and SVRI, but not the other hemodynamic effects, persisted for up to 1 h after restoration of air breathing. Although increased oxidative stress has been proposed as a cause of the cardiovascular response to altered oxygenation, we found no significant changes in venous antioxidant or 8-iso-prostaglandin F2α levels. We conclude that both hyperoxia and hypoxia, when present during isocapnia, cause similar changes in cardiovascular function to those described with poikilocapnic conditions.

VARIATIONS IN OXYGEN TENSION beyond the physiological range have complex effects on cardiovascular function. Hypoxia and hyperoxia have been studied extensively and shown to alter heart rate, cardiac output, and vascular resistance (1, 10, 16, 23, 29, 47). A variety of mechanisms contribute to these cardiovascular responses after changes in oxygen tension. Vascular smooth muscle cell tone is directly affected by altered conduction through L-type Ca2+ channels (48), and ATP-sensitive (11) and voltage-dependent K+ channels (7). In addition, oxygen tension may affect release of angiotensin II, with ensuing changes in endothelin-I levels (53). A number of other vasoactive substances are also produced by the endothelium in an oxygen-sensitive manner, including prostaglandins (31), adenosine (26), and nitric oxide (37). Both hyperoxia (18) and hypoxic (27) conditions can increase formation of reactive oxygen species that may subsequently alter cell function by reacting with various cellular components, including cell membranes, enzymes, and ion channels. Reactive oxygen species created in this way may also play fundamental roles in intracellular signaling (13). Hyperoxia also reduces the bioavailability of nitric oxide, via production of superoxide anions (41). Finally, changes in autonomic balance have been implicated in some of the cardiovascular responses, with hypoxia leading to sympathetic activation (55), whereas hyperoxia reduces sympathetic (43) and possibly increases parasympathetic tone (28, 47).

Many of the previous studies of changes in oxygenation in intact organisms, particularly those investigating hyperoxia, are hard to interpret because carbon dioxide levels were not controlled. This is important because carbon dioxide has profound effects on cardiovascular function through local vascular, chemoreceptor-mediated, and central effects (38). Both hyperoxia and hypoxia stimulate ventilation and reduce arterial carbon dioxide tension (14, 23). It is therefore possible that some of the changes attributed to alterations in oxygen tension may in fact be caused by these secondary changes in ventilation. This potential confounding effect was addressed in part in some previous studies of hypoxia under stable carbon dioxide conditions (40, 44). These studies suggested that short periods of isocapnic hypoxia had smaller but similar effects on cardiovascular function than hypoxia when carbon dioxide is not controlled. Although there have been a number of studies suggesting that hyperoxia reduces heart rate and cardiac output, and increases vascular resistance and vascular stiffness (16, 29, 42, 47), no studies with the primary aim of investigating the cardiovascular consequences of hyperoxia have been carried out under isocapnic conditions.

The main aim of this study was to investigate the cardiovascular effects of both hyperoxia and hypoxia in strict isocapnic conditions. We hypothesized that the changes in cardiovascular function that occur during hyperoxia and hypoxia would not be the same when carbon dioxide levels were held constant. We also studied the time course of changes in cardiovascular function after return to a normal inspired oxygen concentration because others observed that vascular resistance was increased for some time after hyperoxia (15, 47) and that hypoxia caused prolonged activation of the sympathetic nervous system (55). In addition, we wished to explore the
cardiovascular changes that occur if hypoxia is followed by hyperoxia rather than air, mimicking a clinical situation that may occur when hypoxia is treated with high-flow oxygen. We hypothesized that alterations in cardiovascular function resulting from hypoxic and hyperoxic conditions would persist after return to normoxia and that the magnitude of alteration in cardiovascular responses after a period of hypoxia would differ if either normoxic or hyperoxic conditions were applied.

Finally, because any changes in cardiovascular function could be mediated by increased production of reactive oxygen species (18, 27), we investigated the hypothesis that altering inspired oxygen tension increases levels of oxidative stress leading to reductions in plasma antioxidant levels or increases in 8-iso-prostaglandin F2α concentration, a marker of lipid peroxidation (8).

**METHODS**

**Subjects**

Approval for the study was granted by the local research ethics committee, and investigations were carried out in accordance with the principles of the Declaration of Helsinki. We recruited eight healthy men (Table 1) from a community volunteer database held at the Western General Hospital, Edinburgh. Written, informed consent was obtained from all subjects. Subjects were excluded if they had any history of cardiopulmonary, renal, hepatic, or neurological disease. All subjects were nonsmokers, and none was taking regular medications, vitamins, or antioxidant supplements. Subjects were asked to refrain from drinking tea or coffee and from taking any over-the-counter medications for 8 h before each study. In addition, they were asked to abstain from alcohol for 24 h before each study.

**Study Design**

All studies were carried out in a quiet, temperature-controlled room maintained at 22–24°C. Subjects attended on five different occasions, at least 1 wk apart, in a randomized, placebo-controlled, single-blind, crossover study. On each visit the subject reported at 9 AM. Monitors and face mask were applied and a venous cannula (18 gauge) was inserted into a large subcutaneous vein in the left antecubital fossa to allow blood sampling. Subjects then rested semirecumbent on a bed and face mask were applied and a venous cannula (18 gauge) was inserted into a large subcutaneous vein in the left antecubital fossa to allow blood sampling. Subjects then rested semirecumbent on a bed for the duration of the study. Two sets of hemodynamic recordings, separated by 5 min, were made at the end of the 30-min run-in period during which air was breathed, and the mean values were used to represent baseline. The subject was then exposed to three consecutive 1-h periods during which the oxygen tension was varied (normoxia, hypoxia, or hyperoxia), but the end-tidal carbon dioxide tension was held constant. These included the following sequences (1 to 5, respectively) in random order: normoxia-normoxia-normoxia, normoxia-hypoxia-normoxia, normoxia-hyperoxia-normoxia, hypoxia-hyperoxia-normoxia, and hypoxia-normoxia-normoxia. Throughout each phase of the study, hemodynamic recordings were made in duplicate at predetermined intervals and mean values were calculated. During the first hour, recordings were made at 45 and 55 min. More intensive recordings were made during the second hour, at 5, 15, 30, and 55 min, and during the third hour recordings were made at 5, 30 and 55 min. Venous blood was sampled at the end of each hour.

**Administration and Monitoring of Gas Mixtures**

Subjects breathed gas mixtures via a silicone rubber face mask connected to a large two-way nonrebreathing valve and T-piece assembly (Hans Rudolph, Kansas City, MO). Medical-quality oxygen, nitrogen, carbon dioxide, and air (Linde Gas UK, West Bromwich, UK) were delivered by a specially constructed system (Department of Medical Physics, Western General Hospital, Edinburgh, UK) that incorporated computer-controlled mass flow control valves (Bronkhorst HiTec, Ruurlo, Netherlands) and allowed rapid, precise changes in gas composition to be made. Gas in the mask was sampled continuously by a respiratory gas analyzer (Nromocap 200, Datex-Ohmeda, Helsinki, Finland) to measure oxygen and carbon dioxide concentrations. Hyperoxic and hypoxic conditions were created at different stages of studies. Hyperoxia was produced by adding oxygen to the inspired gas mixture to obtain an end-tidal O2 concentration of 85%. This value was chosen as the one that might be reliably achieved and accurately controlled in all subjects. Hypoxia was produced by adding nitrogen to the inspired gas mixture to reduce the pulse oximeter oxygen saturation value to 80%. This saturation was chosen as it could be achieved and sustained with minimal symptoms in healthy volunteers for the duration of the study (56). Normoxia was provided by air breathing through the mask, giving an inspired O2 concentration of 21%. During each 3-h study period the end-tidal CO2 value was held constant at the value noted at the end of a 30-min air-breathing run-in period by adding CO2 to the inspired gas.

**Measurements**

Electrocardiogram and heart rate (Diascope I, S&W Medico Teknik, Albertslund, Finland), pulse oximeter saturation (Satlite Plus, Datex-Ohmeda), and cardiac index (CI) and stroke index (SI) (EXT-TEBCO thoracic electrical bioimpedance monitor, Meko Sapiens, Sedona, AZ) were monitored continuously during the study. Brachial blood pressure was recorded at set intervals by using a semiautomated noninvasive oscillometric sphygmomanometer (Omron HEM-705CP, Omron, Matsuoka, Japan) (33), and mean arterial pressure was calculated as diastolic blood pressure plus 1/3 pulse pressure. Systemic vascular resistance index (SVRI) was calculated by dividing mean arterial pressure by CI. Augmentation index (AI), a marker of arterial stiffness (35), was assessed by computerized pulse wave analysis (Sphygmocor, PWV Medical, West Ryde, Australia) of radial arterial waveforms recorded using a high fidelity applanation tonometer (SPC-301, Millar Instruments, Houston, TX).

**Venous Blood Sampling and Analysis**

At the end of each hour we sampled 50 ml of venous blood into the following tubes (Sarstedt, Leicester, UK): serum gel for total antioxidant quantification and urate analysis, sodium citrate (containing additional 10 µM indomethacin and 0.1 mM butylated hydroxytoluene) for 8-iso-prostaglandin F2α analysis, and lithium heparin for vitamin C analysis. The samples were placed on ice before being....

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<thead>
<tr>
<th>Table 1. Summary of subject characteristics</th>
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<td>Age, yr</td>
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<td>Height, m</td>
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<td>Weight, kg</td>
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<td>BMI, kg/m²</td>
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<td>FEV₁, l/s</td>
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<td>FVC, liters</td>
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<tr>
<td>FEV₁/FVC</td>
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<tr>
<td>HR, beats/min</td>
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<tr>
<td>PSBP, mmHg</td>
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<tr>
<td>PDBP, mmHg</td>
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<tr>
<td>Cardiac index, 1·min⁻¹·m⁻²</td>
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<tr>
<td>Augmentation index, %</td>
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<tr>
<td>Serum creatinine, µmol/l</td>
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<tr>
<td>Plasma glucose, mmol/l</td>
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<td>Serum cholesterol, mmol/l</td>
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<td>Hemoglobin, g/l</td>
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Values are median (range); means ± SE. BMI, body mass index; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; HR, heart rate; PSBP, peripheral systolic blood pressure; PDBP, peripheral diastolic blood pressure.
centrifuged at 2,000 g for 30 min. All plasma and serum were then stored at −80°C before assay. Plasma for vitamin C analysis was stored in the presence of 5% metaphosphoric acid. The total antioxidant activity of serum samples was measured by an enhanced chemiluminescent assay (49) and was expressed as Trolox equivalents (μmol/l). Serum urate concentrations were measured by a colorimetric enzymatic method (20) on a Vitros system (Johnson and Johnson Clinical Diagnostics, Rochester, NY). Plasma vitamin C levels were determined by a colorimetric enzymatic method (4) on a Cobas-Bio analyzer (Roche Diagnostic Systems, Montclair, NJ). Plasma 8-iso-prostaglandin F$_{2\alpha}$ levels were measured by an ELISA (Cayman Chemical, Ann Arbor, MI) after initial preparation by solid-phase extraction using Isosolute C18(EC) 100 mg/3 ml silica-sorbent columns (International Sorbent Technology, Hengoed, Mid Glamorgan, UK). 8-Isoprostaglandin F$_{2\alpha}$ was subsequently eluted with ethylacetate containing 1% methanol.

Data Analysis and Statistics

The study population size, based on a power calculation derived from previous data (47), gave 84% power of detecting a 10% change in AI at a significance level of 5%. Data were examined, where appropriate, by two-factor ANOVA for repeated measures on time and single-factor ANOVA for repeated measures using Excel (Microsoft). Bonferroni correction was used to assess significance at specific time points. All results are presented as means ± SE. Statistical significance was taken at the 5% level.

RESULTS

Gas and Respiratory Measurements

The mean peripheral O$_2$ saturation during the hypoxic periods was 82.6 ± 0.3%. Inspired O$_2$ concentration was reduced to 11.0 ± 0.3% to obtain these values. During the episodes of hypoxia, an end-tidal O$_2$ concentration of 79.6 ± 2.0% was achieved by increasing the inspired O$_2$ concentration to 86.6 ± 1.0%. During each study sequence (1–5), end-tidal CO$_2$ was maintained at a constant value (Table 2), and there was no significant difference between periods during each study sequence (single-factor ANOVAs). CO$_2$ was added to the inspired gas mixture to maintain a constant end-tidal CO$_2$ during each study (Table 2).

Cardiovascular Measurements

Heart rate. Hypoxia reduced the heart rate (mean = -6.7 ± 0.7 beats/min; -10.3 ± 1.0%) (P < 0.001). This was apparent after 5 min and persisted during the hour of hypoxic exposure (Fig. 1A). Conversely, hypoxia caused an increase in heart rate (mean 11.7 ± 0.8 beats/min; 18.2 ± 1.2%) (P < 0.001) that resolved rapidly after correction of hypoxia (Fig. 1A and B).

The bradycardia seen during hyperoxia also occurred when hypoxia was induced after 1 h of hypoxia (P < 0.001, Fig. 1B, 2nd hour).

Blood pressure. No consistent changes were noted in systolic, diastolic, or mean arterial pressure during either hypoxia or hyperoxia. A small increase in pulse pressure (mean 5.5 ± 0.9 mmHg; 13.2 ± 2.3%) was noted during each period of hypoxia (P = 0.02, sequence 2; P < 0.01, sequence 4; P = 0.02, sequence 5).

SI. SI decreased during hyperoxia (mean = -5.2 ± 0.9 ml/min$^2$; -7.3 ± 1.3%) (P < 0.001, Fig. 1C, 2nd hour).

CI. CI decreased during hyperoxia (mean = -0.58 ± 0.05 l/min$^{-1}$·m$^{-2}$; -10.3 ± 1.7%) (P < 0.001, Fig. 1E, 2nd hour) and remained reduced during the subsequent hour of air inhalation (P < 0.01, Fig. 1E, 3rd hour). Conversely, CI increased during hypoxia (mean 0.80 ± 0.08 l/min$^{-1}$·m$^{-2}$; 20.2 ± 1.8%) (P < 0.001, Fig. 1E, 2nd hour; P < 0.001, Fig. 1F, 1st hour). When hypoxia was corrected, the decrease in CI was more marked when a hyperoxic gas mixture was used (P < 0.001, Fig. 1F, 2nd hour).

SVRI. SVRI increased during hyperoxic exposure (mean 3.82 ± 0.46 arbitrary units; 18.9 ± 1.9%) (P < 0.001, Fig. 2A, 2nd hour) and remained greater during subsequent air breathing (P < 0.001, Fig. 2A, 3rd hour). SVRI fell during hypoxia (mean -3.24 ± 0.27 arbitrary units; -15.2 ± 1.2%) (P < 0.001, Fig. 2A, 2nd hour; P < 0.001, Fig. 2B, 1st hour). The correction of the reduced SVRI was greater with hyperoxia than with air (P < 0.001, Fig. 2B, 2nd hour).

AI. AI fell markedly during hypoxia (mean = -10.7 ± 1.1%) (P < 0.001, Fig. 2C, 2nd hour; P < 0.001, Fig. 2D, 1st hour). Hypoxia had no significant effect on AI after a period of air breathing. However, when hypoxic conditions followed hypoxia, a brisker return to baseline values was observed (P < 0.01, Fig. 2D, 2nd hour) than when air was inhaled.

Venous Antioxidant and 8-Isoprostaglandin F$_{2\alpha}$ Measurements

Neither hypoxia nor hypoxia affected the serum antioxidant capacity, serum urate concentration, or plasma vitamin C concentration during any of the study sequences (Table 3). Similarly, there were no consistent, significant changes in the plasma concentrations of 8-iso-prostaglandin F$_{2\alpha}$ during each sequence of varied inspired oxygen tension.

DISCUSSION

This study investigates the cardiovascular responses to both hypoxia and hyperoxia under strict isocapnic conditions. For
the first time, we demonstrate that 1-h episodes of isocapnic hyperoxia lead to significant alterations in heart rate, CI, and vascular resistance. Furthermore, we show that isocapnic hypoxia has effects on CI and vascular resistance that persist for up to 1 h after a return to normoxic conditions. We have also shown that large artery stiffness, assessed as the aortic AI, measured by pulse-wave analysis, is significantly reduced in response to isocapnic hypoxia whereas, in contrast, isocapnic hyperoxia has little effect. The other major new finding is that the cardiovascular response during recovery from hypoxia is significantly influenced by the inspired oxygen concentration with greater changes in heart rate, cardiac output, and vascular resistance produced by hyperoxic gas mixtures.

Cardiovascular Effects of Isocapnic Hyperoxia and Hypoxia

Isocapnic hyperoxia caused similar reductions in heart rate \((-10.3 \pm 1.7\%\); mean over 1 h exposure) and CI \((-10.3 \pm 1.7\%\) as those reported in previous studies that did not control carbon dioxide \((1, 10, 22, 23, 47, 50)\). The decreased cardiac output was not entirely caused by reduced heart rate because SI decreased by 7.3 \(\pm 1.3\%\). Only one previous study has shown...
that hyperoxia reduced SI in healthy subjects (50). Hyperoxia has more consistently reduced SI in studies of subjects with congestive cardiac failure (16, 29, 42), suggesting that these patients may be more sensitive, or respond differently, to hyperoxia. Of particular interest in our study were the persistent effects of hyperoxia on CI and SVRI after the inspired oxygen concentration had been reduced to normal. This supports two previous studies that showed that peripheral vascular resistance remained increased for 30–40 min after stopping of 100% oxygen inhalation (15, 47).

The cardiovascular effects of isocapnic hypoxia are similar to those seen in previous studies of hypoxia where variations in carbon dioxide were permitted (1, 3, 12, 23). Heart rate (18.2 ± 1.2%), CI (20.2 ± 1.8%), and pulse pressure (13.2 ± 2.3%) increased along with a decrease in SVRI (−15.2 ± 1.2%). CI increased because of an increase in heart rate, as SI did not alter.

![Fig. 2. Vascular resistance and stiffness measurements. A and B: hyperoxia created a rise in systemic vascular resistance index (SVRI; sequence 3, P < 0.001) that persisted during air inhalation (P < 0.001) while hypoxia caused a reduction in SVRI (sequences 2, 4, and 5, P < 0.001). C and D: hypoxia produced a marked reduction in augmentation index (AI; sequences 2, 4, and 5, P < 0.001). The lowered AI produced by hypoxia was corrected more rapidly when hyperoxic conditions were imposed (sequence 4, P < 0.01). au, Arbitrary units.](image)

Table 3. Venous antioxidant and 8-iso-prostaglandin F2α levels

<table>
<thead>
<tr>
<th>Study Sequence</th>
<th>Total Antioxidant Activity</th>
<th>Serum Urate, µM/1</th>
<th>Plasma Vitamin C, µM/1</th>
<th>Plasma 8-iso-PGF2α, pg/ml</th>
</tr>
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<tr>
<td></td>
<td>Trolox Equiv, µM/1</td>
<td>1st Hour 2nd Hour 3rd Hour</td>
<td>1st Hour 2nd Hour 3rd Hour</td>
<td>1st Hour 2nd Hour 3rd Hour</td>
</tr>
<tr>
<td>1 N 2 N Hypo</td>
<td>415.4 ± 27.4 397.7 ± 28.8</td>
<td>335.1 ± 24.5 358.3 ± 26.2</td>
<td>317.9 ± 24.7 376.5 ± 24.9</td>
<td>36.8 ± 5.0 41.9 ± 6.1</td>
</tr>
<tr>
<td>2 N Hypo</td>
<td>407.9 ± 21.3 408.1 ± 32.8</td>
<td>345.3 ± 19.1 337.6 ± 19.9</td>
<td>58.1 ± 3.7 57.2 ± 3.5</td>
<td>38.1 ± 5.2 41.0 ± 5.7</td>
</tr>
<tr>
<td>3 N Hyper</td>
<td>385.4 ± 18.3 382.4 ± 23.6</td>
<td>325.9 ± 14.4 327.1 ± 15.3</td>
<td>70.3 ± 5.7 65.6 ± 6.5</td>
<td>40.5 ± 4.9 35.9 ± 5.0</td>
</tr>
<tr>
<td>4 Hypo</td>
<td>364.9 ± 17.4 379.6 ± 19.4</td>
<td>313.6 ± 14.2 328.5 ± 19.7</td>
<td>64.7 ± 7.4 66.8 ± 4.8</td>
<td>34.4 ± 7.7 31.6 ± 3.3</td>
</tr>
<tr>
<td>5 N Hypo</td>
<td>435.5 ± 29.3 405.3 ± 19.3</td>
<td>427.3 ± 23.4 377.9 ± 24.7</td>
<td>63.1 ± 3.3 64.8 ± 5.2</td>
<td>34.6 ± 4.6 29.7 ± 2.8</td>
</tr>
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Values are means ± SE. Equiv., equivalent. There were no significant changes in total antioxidant activity, urate, vitamin C, or 8-iso-prostaglandin F2α levels during any of the study sequences.
In conclusion, carefully controlling carbon dioxide levels during both hyperoxia and hypoxia has little influence on the changes in heart rate, cardiac output, and systemic vascular resistance produced by alterations in oxygenation.

Assessment of the Effects of Changes in Oxygenation on Vascular Stiffness Using Pulse-Wave Analysis

Systolic pulse contour analysis is frequently used to determine arterial stiffness, an important determinant of cardiovascular risk (35). Peripheral arterial pressure waveforms are recorded noninvasively by using applanation tonometry and are transformed into corresponding central pressure waveforms by using a transfer factor. AI, a commonly used measure of arterial stiffness, is then calculated from the derived central aortic waveforms. AI is influenced by both the timing and intensity of reflected pressure waves returning to the proximal aorta. Increased AI is associated with a number of risk factors for cardiovascular disease including hypercholesterolemia and Type I diabetes mellitus. It can also be altered acutely by infusion of vasoconstrictor (52) and vasodilator drugs (34). For the first time, we quantified the effects of isocapnic hypoxia on arterial stiffness by using pulse-wave analysis to measure AI. Isocapnic hypoxia reduced AI (mean $-10.7 \pm 1.1\%$), even allowing for the contribution that an increase in heart rate may have had (51). This reduction in AI is similar to changes caused by clinically relevant doses of nitrates (34) and implies that the vasodilatation produced by hypoxia may affect arterial stiffness or the amplitude or site of wave reflection throughout the arterial tree (21). In contrast, isocapnic hyperoxia had little effect on AI. This was surprising, because we previously found that when carbon dioxide levels were not controlled, hyperoxia increased AI markedly (47). Changes in carbon dioxide tension can affect arteriolar resistance (38), so the increased AI during poikilocapnic hyperoxia could be caused by the hypocapnia that results from stimulation of ventilation. To confirm these findings, further studies of arterial stiffness that directly compare poikilocapnic with isocapnic conditions are required. In addition, the specific effects of changes in carbon dioxide on AI should be established.

Importance of Inspired Oxygen Concentration in Determining the Magnitude of Cardiovascular Responses After Hypoxia

A further aim of this study was to determine whether there were any significant differences in cardiovascular function during recovery from hypoxia if this occurred during hyperoxic rather than normoxic conditions. This is an important issue in clinical practice as hyperoxia is often produced unintentionally in patients who were previously hypoxic. This occurs because high-flow oxygen therapy is often administered by variable-performance face masks (25) and monitoring of its effects is frequently inadequate (46). We found that correcting arterial hypoxia with a hyperoxic gas mixture had more marked effects on heart rate, CI, SVRI, and AI than when air was used. This finding is clinically relevant because hyperoxia-induced increases in vascular resistance and reductions in cardiac output may be detrimental in the context of critical illness.

Effects of Isocapnic Hyperoxia and Hypoxia on 8-Iso-Prostaglandin F$_{2\alpha}$ and Antioxidant Levels

The exact mechanisms underlying the physiological responses to hyperoxia and hypoxia have yet to be clearly defined. However, increased production of reactive oxygen species and oxidative stress may play a role (18, 36, 54). We investigated this possibility by measuring plasma 8-iso-prostaglandin F$_{2\alpha}$, a reliable marker of lipid peroxidation (8) that is formed by a free radical-catalyzed modification of arachidonic acid within cell membranes. Vitamin C and urate, the two most important extracellular antioxidants, were also measured, as was total antioxidant activity, a global measure of serum antioxidant capacity. Hypoxia, hyperoxia, or the combination of hyperoxia after hypoxia had no effect on these parameters. The lack of effect on plasma 8-iso-prostaglandin F$_{2\alpha}$ levels is of interest because it is not only a marker of oxidative stress but it also causes vasoconstriction (19) and could have contributed to the persistent vasoconstrictive effect of hyperoxia. These results suggest that the short-term variations in oxygen tension in our studies, which did have major hemodynamic effects, did not impose a significant oxidative stress. However, it should be acknowledged that such changes could have been too small to measure systemically or may have occurred in regional circulations, in the microcirculation, or in the lung. For example, in the study conducted by Carpagnano et al. (5), small increases in 8-isoprostane levels were found in exhaled breath condensate after 1 h of 28% oxygen inhalation in both healthy subjects and patients who had chronic obstructive pulmonary disease. It is also possible that healthy subjects may have sufficient antioxidant reserves to buffer small changes in oxidative stress so that venous measurements of 8-iso-prostaglandin F$_{2\alpha}$ and antioxidants may be insufficiently sensitive to detect small degrees of oxidative stress.

Limitations

An important component of this study was to ensure that carbon dioxide values did not change while we studied the effects of altered oxygen tension. We met this requirement, but to do so carbon dioxide needed to be added to the inspired gas mixture during both hyperoxia and hypoxia. This is obligatory in a study that aims to maintain normocapnia despite increased ventilation. We did not formally measure minute ventilation, but it is known that both hyperoxia and hypoxia stimulate ventilation and that this is greater under isocapnic conditions (2, 17). Because inspired carbon dioxide was necessary to maintain stable end-tidal conditions, an increase in minute ventilation was implied. Ventilation changes might affect the use of impedance for measuring cardiac output. However, impedance cardiography has been used successfully to monitor changes in cardiac output in healthy men during exercise in which large changes in ventilation would be present (32, 45), and we considered the method appropriate for this study. Ventilation can affect the overall cardiovascular response to hypoxia. In anesthetized dogs, hypoxic stimulation of the carotid body causes tachycardia at high ventilation values, but bradycardia at lower values (9). This is thought to relate to the level of pulmonary stretch receptor activity and the interrelationship of respiratory, cardiovascular, and chemoreceptive areas in the ventrolateral medulla and the nucleus tractus solitarius (30). We could not assess how changes in ventilation...
affected the cardiovascular effects found in our study; however, because isocapnic environments cause greater increases in ventilation than poikilocapnic conditions it is possible to speculate that this relative hyperventilation may have influenced vascular resistance and AI, as voluntary hyperventilation has previously been shown to reduce forearm vascular resistance (6).

In this study, we chose to investigate the effects of changes in oxygenation on cardiovascular function in male subjects only. This allowed us to compare these effects with those documented previously in studies that did not control carbon dioxide tension because they used male subjects either exclusively, or in marked majorities over female subjects. Studying only male subjects under isocapnic conditions means that it is difficult to extrapolate our results, and studies investigating the hemodynamic effects of altered oxygen tension female subjects are required.

Clinical Relevance

The risks of hypoxia have been appreciated for many years, yet we still need to define the optimal use of oxygen therapy more than two centuries after it was first used. In one of the few randomized, double-blind, controlled trials of oxygen therapy, patients with uncomplicated myocardial infarction randomized to receive supplemental oxygen tended to have a higher mortality and more ventricular tachycardia than those randomized to air (39). In addition, previous studies of patients with severe congestive heart failure (16, 29, 42) suggested that oxygen therapy must be used carefully because hyperoxia has potentially undesirable hemodynamic effects. Routine use of supplemental oxygen at caesarean section performed under regional anesthesia has also been questioned after increased levels of lipid peroxidation were noted in the fetoplacental unit with little improvement in umbilical oxygenation (24). Although the isocapnic design of our study makes it impossible to make direct clinical recommendations, we have confirmed that hyperoxia, even after an episode of hypoxia, has significant effects on the human circulation. The cardiovascular effects of hyperoxia after hypoxia need to be confirmed under poikilocapnic conditions.

In conclusion, in this study we found that many of the hemodynamic changes of hypoxia and hyperoxia are also present when carbon dioxide tension is controlled. However, we also found that the effects of isocapnic hyperoxia on arterial stiffness were different from when carbon dioxide was allowed to change. This suggests that altered carbon dioxide tensions may contribute to some of the cardiovascular effects of hyperoxia. This requires confirmation in a study that compares isocapnic and poikilocapnic conditions directly. Finally, we have confirmed that hyperoxia has long-lasting cardiovascular effects that may be clinically relevant when using oxygen therapy.

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REFERENCES

HEMODYNAMIC EFFECTS OF OXYGEN


