EFFECTS OF SUPPLEMENTAL OXYGEN ADMINISTRATION ON CORONARY BLOOD FLOW IN PATIENTS UNDERGOING CARDIAC CATHETERIZATION

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McNulty, Patrick H., Nicholas King, Sofia Scott, Gretchen Hartman, Jennifer McCann, Mark Kozak, Charles E. Chambers, Laurence M. Demers, and Lawrence I. Sinoway. Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. Am J Physiol Heart Circ Physiol 288: H1057–H1062, 2005; doi:10.1152/ajpheart.00625.2004.—Patients with heart disease are frequently treated with supplemental oxygen. Although oxygen can exhibit vasoactive properties in many vascular beds, its effects on the coronary circulation have not been fully characterized. To examine whether supplemental oxygen administration affects coronary blood flow (CBF) in a clinical setting, we measured in 18 patients with stable coronary heart disease the effects of breathing 100% oxygen by face mask for 15 min on CBF (via coronary Doppler flow wire), conduit coronary diameter, CBF response to intracoronary infusion of the endothelium-dependent dilator ACh and to the endothelium-independent dilator adenosine, as well as arterial and coronary venous concentrations of nitric oxide (NO) metabolites nitrotyrosine, NO2⁻, and NO3⁻. Relative to breathing room air, breathing of 100% oxygen increased coronary resistance by ~40%, decreased CBF by ~30%, increased the appearance of nitrotyrosine in coronary venous plasma, and significantly blunted the CBF response to ACh. Oxygen breathing elicited these changes without affecting the diameter of large-conduit coronary arteries, coronary venous concentrations of NO2⁻ and NO3⁻, or the coronary vasodilator response to adenosine. Administering supplemental oxygen to patients undergoing cardiac catheterization substantially increases coronary vascular resistance by a mechanism that may involve oxidative quenching of NO within the coronary microcirculation.

ADMINISTRATION OF SUPPLEMENTAL OXYGEN TO PATIENTS WITH CORONARY HEART DISEASE (CHD) IS A COMMONCLINICAL PRACTICE (23). In healthy subjects, high arterial blood oxygen tension has been demonstrated to be a vasoconstrictor stimulus in the forearm (7, 17) and systemic vasculatures (8, 19) and acts by a mechanism believed to involve oxidative inactivation of endothelium-derived relaxation factors including nitric oxide (NO; Refs. 7, 8, 29). Whether this mechanism operates in the human coronary circulation is not known. Indeed, it might be expected that patients with CHD are relatively insensitive to this vasoconstrictor effect by virtue of the fact that the coronary endothelium of such patients has impaired ability to generate NO in response to physiological and pharmacological stimuli (1, 28, 33). In this study, we used intracoronary Doppler flow recording and measurement of arterial and coronary venous concentrations of NO oxidation (NO2⁻ and NO3⁻) and peroxidation (nitrotyrosine) products to examine this question in a group of patients with stable CHD who underwent diagnostic cardiac catheterization.

METHODS

Subjects. Twenty-seven nondiabetic adult subjects (16 males and 11 females; 43–70 yr old) were studied during elective cardiac catheterization performed to evaluate chest pain. No subject had a coronary stenosis of >50% severity by angiography, and all had a left ventricular ejection fraction of >50%. All subjects were taking both a long-acting β-blocker and aspirin, and 15 subjects were taking a statin, but none were on an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. None of the subjects had experienced chest pain or used nitroglycerin in any form for at least 24 h before the study. The study protocol was approved by the Institutional Review Board of the Pennsylvania State College of Medicine, and subjects gave written informed consent.

Study protocol. Vascular sheaths were placed in a femoral artery and vein under 2% xylocaine local anesthesia. A Simmons-2 catheter was placed into the coronary sinus from the femoral vein to allow arterial-coronary venous blood sampling. Standard transfemoral coronary angiography was performed while subjects were under midazolam and fentanyl sedation. In 12 subjects, a guiding catheter was then placed into either the left (n = 6) or right (n = 6) coronary artery; this was used to introduce a 0.014-in Doppler flow wire (FloMap system; Jomed; Rancho Cordova, CA) into a major coronary branch that was demonstrated by the angiogram to be free of obstructive atherosclerosis. While subjects breathed room air, paired samples of arterial and coronary venous blood were obtained for measurement of blood gases, hemoglobin, and the NO metabolites NO2⁻ and NO3⁻. Doppler coronary flow velocity (CFV, measured in cm/s) was then recorded with subjects at rest and after intracoronary infusion of the endothelium-independent dilator adenosine (20 µg for right coronary or 40 µg for left coronary studies; Fujisawa). In five subjects whose coronary angiograms were nearly free of atherosclerosis, the effect on CFV of the endothelium-dependent dilator ACh (Clinalfa), which was administered by serial 3-min infusions of a 20 µg/ml solution through the guiding catheter at 0.5 and 1.0 ml/min, was also measured. To allow for conversion of CFV to coronary blood flow (CBF, measured in cm³/min) values, we measured the diameter of the coronary segment that held the Doppler wire from the angiogram with electronic calipers while using the diameter of the guiding catheter as a reference.
reference. After completion of these measurements, subjects breathed 100% oxygen via a standard reservoir-bag mask for 15 min, and all measurements were repeated. In six subjects, the 15-min period of 100% oxygen breathing was followed by a subsequent 20-min recovery period in which subjects again breathed room air. CFV was monitored through this recovery period to examine the persistence of hyperoxic changes in coronary resistance and blood flow. To control for nonspecific changes in CFV over time, in three additional subjects, CFV was monitored during a 30-min period of room-air breathing without exposure to 100% oxygen.

Chemical analyses. Partial pressures of oxygen (PO2) and carbon dioxide (PCO2) and pH were measured in whole blood with a Bayer blood gas analyzer. Blood oxygen saturation was measured by reflectance oximetry. Coronary NO production was estimated by measuring arterial and coronary venous concentrations of the NO metabolites NO2- and NO3- with a Sievers 180i NO analyzer. With the use of this method, NO2- [produced in vivo by direct oxidation of NO (9)] and NO3- [produced in vivo as a product of the reaction of NO with oxyhemoglobin (9)] are quantitatively reduced to NO by boiling in vanadium trichloride, and the NO gas thus liberated is reacted with ozone and quantified by chemiluminescence (36). Our assay method attempted to account for the fact that NO released by vascular endothelial proteolysis. The minimal detection level for the nitrotyrosine ELISA was 1 pg/ml. Between-run precision was 10% for both assays.

Calculations. CBF (measured in cm3/min) was calculated by multiplying CFV (measured in cm/s) by the cross-sectional area (π × arterial radius2) of the coronary artery 5 mm distal to the tip of the Doppler wire and the factor 0.5 (1). Coronary vascular resistance [CVR, measured in mmHg/(min/cm3)] was calculated by dividing the difference between mean arterial pressure and coronary sinus pressure by CBF. Blood oxygen content (measured in ml/l) was calculated by multiplying the blood hemoglobin concentration (measured in g/l) by the oxygen-carrying capacity of hemoglobin (1.36 ml/g) and the blood oxyhemoglobin saturation. The regional myocardial oxygen consumption rate (MV.O2, measured in ml/min) was calculated by multiplying the arterial-coronary venous difference for blood oxygen content (in ml/l) by CBF (in l/min).

RESULTS

Hemodynamics. Breathing 100% oxygen had no consistent effect on heart rate, blood pressure, or the diameter of the large-conduit coronary arteries [3.3 ± 0.4 vs. 3.2 ± 0.3 mm; P = not significant (NS)] but did reduce CFV in each subject from 20 ± 6 to 14 ± 6 cm/s (P < 0.01; Fig. 1). This reduction was apparent within 5 min and corresponded to a 29% decrease in calculated CBF (from 45 ± 14 to 32 ± 7 cm3/min; P < 0.01) and a 41% increase in calculated CVR [from 2.2 ± 0.7 to 3.1 ± 0.9 mmHg/(min/cm3); P < 0.01]. In three control subjects not exposed to 100% oxygen, CFV deviated by <10% from baseline during a 30-min period of room-air breathing. Among subjects who were observed for 20 min after discontinuing 100% oxygen breathing, three demonstrated a prompt (<5 min) return of CFV to the original baseline value, whereas in the other three, CFV remained depressed throughout the observation period. Individual data for CFV, CBF, and CVR are shown in Fig. 2.

Oxygen and NO. Data for the blood gas results and MV.O2 are shown in Table 1. Breathing 100% oxygen increased arterial PO2 from 73 ± 9 to 273 ± 43 mmHg and arterial oxygen saturation from 93 ± 4 to 100%. Coronary venous oxygen saturation simultaneously increased from 32 ± 3 to 38 ± 5% so that the arterial-coronary venous difference for oxygen content did not change. Because CBF decreased during 100% oxygen breathing, calculated regional MV.O2 decreased from 5.2 ± 0.6 to 3.8 ± 0.4 ml/min. During room-air breathing, the concentration of free NO2- and NO3- ([NO2- + NO3-])...
in arterial and coronary venous blood lysates averaged 75 ± 15 and 80 ± 17 μM, respectively (P = NS). Heating blood lysates to release protein-bound NO increased the free [NO₂⁻ + NO₃⁻] by only 10–15%. Breathing 100% oxygen did not significantly change arterial or coronary venous free [NO₂⁻ + NO₃⁻] or protein-bound NO. As a consequence of reducing CBF, 100% oxygen breathing did reduce absolute cardiac efflux of NO₂⁻ and NO₃⁻, which was calculated as the product of CBF and coronary venous [NO₂⁻ + NO₃⁻], from 3.5 ± 1.0 to 2.4 ± 0.6 μmol/min (P < 0.01).

Nitrotyrosine and endothelin-1. During room-air breathing, arterial and coronary sinus plasma nitrotyrosine concentrations averaged 394 ± 344 (SD) and 374 ± 340 nM, respectively, and no consistent net consumption or production of nitrotyrosine was observed across the heart (coronary sinus-arterial concentration difference, 19 ± 75 nmol/l; P = NS vs. zero). During 100% oxygen breathing, coronary sinus nitrotyrosine concentrations rose in 10 of the 12 subjects examined (to 461 ± 479 nM; P = 0.21 vs. room air), and all 12 subjects exhibited higher nitrotyrosine levels in the coronary sinus compared with arterial plasma levels (coronary sinus-arterial concentration difference, 126 ± 189 nmol/ml; P = 0.003 vs. room-air breathing; Fig. 3). Plasma endothelin-1 concentrations were below the detection limit of the assay in 9 of the 12 subjects, and no consistent effects of 100% oxygen breathing on coronary sinus endothelin-1 level or endothelin-1 arterial-coral sinus difference were observed.

Adenosine and ACh responses. Although 100% oxygen breathing reduced resting CBF, oxygen administration did not affect the magnitude of the CBF response to the endothelium-independent dilator adenosine; thus postadenosine CBF averaged 108 ± 34 cm³/min with subjects breathing room air vs. 108 ± 32 cm³/min with subjects breathing 100% oxygen (P = NS). In contrast, oxygen administration blunted the CBF response to the endothelium-dependent dilator ACh to the same degree that it reduced resting CBF. Thus as shown in Fig. 4, ACh administration produced a dose-dependent increase in CBF during both room-air and 100% oxygen breathing, but the absolute magnitude of this effect was blunted during 100% oxygen breathing. The ability of 100% oxygen breathing to quench the coronary dilator action of ACh was also evident on coronary angiography as shown in Fig. 5.

DISCUSSION

The administration of high-flow supplemental oxygen by facemask to patients with CHD is a common practice particularly during conscious-sedation procedures in which the performing physician perceives a risk of hypoventilation and hypoxemia. During such procedures, the arterial oxygen content is usually estimated by monitoring transcutaneous blood oxyhemoglobin saturation. Because this technique is insensitive to changes in oxygen tension above the level needed to produce a 100% oxyhemoglobin saturation (Po₂ of ~90 mmHg), the use of high-flow oxygen in this setting can lead to unsuspected degrees of hyperoxia. In this study, administration of supplemental oxygen by face mask to sedated patients undergoing cardiac catheterization increased average arterial Po₂ to >250 mmHg. This was associated with a prompt ~40% increase in coronary resistance and a ~30% decrease in CBF in the absence of any significant change in the diameter of large-conductance coronary vessels. These results suggest that hyperoxia is a potent vasoconstrictor stimulus to the coronary circulation that functions at the level of microvascular resistance vessels.

ACh produces arterial dilation by stimulating the release of NO and other mediators from the vascular endothelium (10), whereas adenosine functions by endothelium-independent ac-
Breathing room air and 100% oxygen. Data are means ± sd; n = 18 subjects. Arterial (Art) and coronary sinus (CS) oxygen partial pressure (PO2), oxyhemoglobin saturation, blood oxygen content, arterial-coronary venous oxygen content difference, and net cardiac oxygen consumption (VO2; arterial-venous oxygen content difference × coronary blood flow) values obtained during room-air and 100% oxygen breathing. Oxygen administration proportionately reduced cardiac oxygen delivery (coronary blood flow) and cardiac oxygen consumption such that transcardiac oxygen extraction (arterial-coronary oxygen content difference) did not change. *P < 0.01 vs. room air.

Table 1. Arterial and coronary sinus oxygen content and myocardial oxygen consumption

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<th>PO2, mmHg</th>
<th>Hemoglobin Saturation, %</th>
<th>Blood O2 Content, ml/l</th>
<th>Art-CS O2 Content, ml/l</th>
<th>Cardiac VO2, ml/min</th>
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<tr>
<td>Room air</td>
<td>Art</td>
<td>CS</td>
<td>Art</td>
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<tr>
<td>73 ± 9</td>
<td>93 ± 4</td>
<td>181 ± 24</td>
<td>119 ± 26</td>
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<tr>
<td>100% Oxygen</td>
<td>273 ± 43*</td>
<td>100*</td>
<td>194 ± 22*</td>
<td>73 ± 21*</td>
<td>120 ± 23</td>
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Values are means ± SD; n = 18 subjects. Arterial (Art) and coronary sinus (CS) oxygen partial pressure (PO2), oxyhemoglobin saturation, blood oxygen content, arterial-coronary venous oxygen content difference, and net cardiac oxygen consumption (VO2; arterial-venous oxygen content difference × coronary blood flow) values obtained during room-air and 100% oxygen breathing. Oxygen administration proportionately reduced cardiac oxygen delivery (coronary blood flow) and cardiac oxygen consumption such that transcardiac oxygen extraction (arterial-coronary oxygen content difference) did not change. *P < 0.01 vs. room air.

tivation of G protein-linked smooth muscle adenosine receptors (11). Thus the observation that hyperoxia attenuated the coronary vasodilator response to ACh but not adenosine suggests that hyperoxia-induced vasoconstriction is mediated by an effect on coronary endothelial function. The most plausible physiological explanation for this effect is that hyperoxia may accelerate the oxidative degradation of coronary endothelium-derived NO by reactive oxygen species (ROS). ROS are generated in vivo under hyperoxic conditions (12) and have been shown to readily degrade NO in vitro (29). The recent observation that hyperoxia-induced vasocstriction of the forearm vasculature can be reduced by pretreatment with an antioxidant (17) supports the idea that this mechanism also operates in vivo in humans.

We wanted to establish and confirm that this hyperoxia-induced vasocstrctor mechanism also functions in hearts of human subjects. We first determined whether hyperoxia affects the arterial-coronary venous balance of free NO2 and NO3 ions or protein-bound NO. We were, however, unable to demonstrate any consistent concentration gradient for these NO species across the coronary circulation either during room-air or 100% oxygen breathing. Although the existence of such a gradient would seem a logical consequence of coronary circulation either during room-air or 100% oxygen breathing. Although the existence of such a gradient would seem a logical consequence of coronary endothelium NO production, we have noted inconsistent findings by other investigators in this regard (3, 14, 27, 33, 37). This inconsistency may reflect a number of factors including

Fig. 3. Arterial and coronary sinus (CS) plasma concentrations and net coronary sinus-arterial concentration difference for nitrotyrosine in subjects breathing room air and 100% oxygen. Data are means ± se for 12 subjects. Breathing 100% oxygen significantly increased net cardiac nitrotyrosine wash-out (coronary sinus-arterial concentration difference) relative to room air breathing.

The observation that breathing 100% oxygen resulted in net cardiac production of nitrotyrosine (i.e., coronary sinus concentration > arterial concentration) in our subjects suggests that oxidative quenching of NO within the coronary microcirculation may contribute to hyperoxic coronary vasocstriction. We note that an elevated systemic nitrotyrosine level was recently shown (30) to be a marker for the presence of atherosclerosis. Because all of our subjects had early coronary atherosclerosis, it is possible that the mechanism responsible

Fig. 4. CFV recorded at baseline (ACh-0) and during intracoronary infusion of 10 and 20 µg/min ACh (ACh-10 and ACh-20, respectively) and 20–40 µg adenosine in five subjects. *P < 0.05 vs. room air.
for the increase we observed in coronary venous nitrotyrosine levels in response to supplemental oxygen operates systemically in these subjects as well.

The observation that CBF and MV/O decreased simultaneously and proportionately in response to hyperoxia in our subjects (Table 1) would appear to confirm the principle that the heart can concordantly regulate oxygen delivery and consumption to balance energy supply and utilization and prevent cardiomyocyte oxygen toxicity (35). On the basis of observations in cultured cells and isolated perfused hearts, this phenomenon has been hypothesized to be mediated by cross-talk between cardiac myocytes and coronary endothelial cells mediated by endothelium-derived (e.g., NO, endothelin-1) and myocyte-derived (e.g., adenosine, angiotensin I) regulatory factors (2, 18, 21, 25, 35). Although little is known about the mechanisms that link CBF and MV/O in humans, our observations suggest that experiments testing the effect of hyperoxia on the coronary venous efflux of such regulatory factors might be a novel way of examining this system in vivo. Based on the observation of Winegrad et al. (35) that culture media from cardiac myocytes exposed to increased Po2 in vitro elicit endothelin-1-mediated vasoconstriction in isolated coronary vessels, we sought to determine whether hyperoxia increased endothelin-1 levels in coronary venous blood in our studies. Although we were unable to detect such an increase, this does not completely exclude a role for this molecule in mediating hyperoxic coronary constriction. For instance, it has been suggested (35) that under some circumstances, endothelin-1 may be released by the vascular endothelium abluminally into the cardiac interstitial space rather than into the bloodstream.

A somewhat surprising implication of our study is that a substantial portion (30%) of CBF in our room-air breathing subjects was hyperoxia sensitive and therefore presumably endothelium dependent. Several studies (1, 28, 34) suggest that the ability of the coronary endothelium to elaborate these relaxing factors becomes compromised early in the development of coronary artery disease. Because all of our subjects had risk factors for CHD and most (n = 24) actually had coronary atherosclerosis severe enough to detect by angiography, it might have been expected that they would have this impairment. One possible confounding variable, however, was the high frequency of statin use by these subjects. Short-term statin treatment increases coronary endothelial NO synthase expression and coronary microvascular NO production in dogs (20) and increases endothelium-dependent forearm blood flow in humans (22). Although the effects of chronic statin use on coronary NO production in humans are unknown, it is conceivable that the use of relatively high doses of these drugs by most of our subjects accounts for their apparently substantial degree of endothelium-dependent coronary relaxation while they breathed room air. Another potential explanation for our findings was recently suggested by Cosby et al. (6), who observed that erythrocytes traversing the forearm circulation can lower forearm vascular resistance by reducing nitrite ions to NO at a rate proportional to their deoxyhemoglobin contents. Were this mechanism to operate in heart (which has not yet been confirmed), it might be predicted that breathing 100% oxygen would tend to increase coronary resistance by increasing hemoglobin oxygen saturation and thereby lowering erythrocyte nitrate reductase activity and NO production.

Limitations. Because of inherent selection bias (we only studied subjects with early coronary atherosclerosis who were undergoing cardiac catheterization for a clinical indication), the relevance of these findings for healthy subjects is uncertain. Practical constraints imposed by the need to perform the study in conjunction with a clinical procedure likewise prevented us from formally characterizing baseline coronary endothelial function in these subjects or withholding certain medications (e.g., aspirin), which may potentially affect endothelial function. Obviously, a complete understanding of the relationship between ambient oxygen tension and coronary resistance in vivo will require the performance of formal dose-response studies.

Clinical implications. The findings of this study suggest that the common clinical practice of administering supplemental oxygen to patients with the goal of maintaining 100% oxygen saturation may increase CVR and reduce CBF. In patients with severe CHD, this could potentially precipitate myocardial ischemia and cardiac dysfunction. The routine administration of high-flow oxygen to such patients may therefore be unwise. Because ROS may have especially adverse effects on the ischemic myocardium (4), the routine administration of supplemental oxygen to patients suffering acute myocardial infarction or undergoing coronary interventions must be viewed with particular skepticism. When administering oxygen to patients with CHD, physicians should recognize that oxygen is itself a vasoactive substance most appropriately dispensed in precise doses titrated against the measured arterial Po2.
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REFERENCES


