Contribution of endothelin to pulmonary vascular tone under normoxic and hypoxic conditions

WENDY JOHNSON,* ANJU NOHRIA,* LESLIE GARRETT, JAMES C. FANG, JAMES IGO, MIYUKI KATAI, PETER GANZ, AND MARK A. CREAGER
Cardiovascular Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts 02115

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Johnson, Wendy, Anju Nohria, Leslie Garrett, James C. Fang, James Igo, Miyuki Katai, Peter Ganz, and Mark A. Creager. Contribution of endothelin to pulmonary vascular tone under normoxic and hypoxic conditions. Am J Physiol Heart Circ Physiol 283: H568–H575, 2002; 10.1152/ajpheart.00099.2001.—The contribution of endothelin to resting pulmonary vascular tone and hypoxic pulmonary vasoconstriction in humans is unknown. We studied the hemodynamic effects of BQ-123, an endothelin type A receptor antagonist, on healthy volunteers exposed to normoxia and hypoxia. Hemodynamics were measured at room air and after 15 min of exposure to hypoxia (arterial PO2 99.8 ± 1.8 and 49.4 ± 0.4 mmHg, respectively). Measurements were then repeated in the presence of BQ-123. BQ-123 decreased pulmonary vascular resistance (PVR) 26% and systemic vascular resistance (SVR) 21%, whereas it increased cardiac output (CO) 22% (all P < 0.05). Hypoxia raised CO 28% and PVR 95%, whereas it reduced SVR 23% (all P < 0.01). During BQ-123 infusion, hypoxia increased CO 29% and PVR 97% and decreased SVR 22% (all P < 0.01). The pulmonary vasoconstrictive response to hypoxia was similar in the absence and presence of BQ-123 [P = not significant (NS)]. In vehicle-treated control subjects, hypoxic pulmonary vasoconstriction did not change with repeated exposure to hypoxia (P = NS). Endothelin contributes to basal pulmonary and systemic vascular tone during normoxia, but does not mediate the additional pulmonary vasoconstriction induced by acute hypoxia.

*W. Johnson and A. Nohria contributed equally to this work.
Address for reprint requests and other correspondence: M. A. Creager, Cardiovascular Div., Brigham and Women’s Hosp., 75 Francis St., Boston, MA 02115 (E-mail: mcreager@partners.org).

THE VASCULAR ENDOTHELIUM plays a pivotal role in the regulation of systemic and pulmonary vascular tone. It elaborates a number of vasoactive factors that act in a paracrine fashion to modulate vascular smooth muscle tone. Abnormalities in vascular smooth muscle tone and proliferation underlie several diseases such as atherosclerosis and pulmonary hypertension. Endothelin-1 (ET-1) is an endothelium-derived, 21-amino acid peptide with potent vasoconstrictor (69, 70) and mitogenic properties (31, 36, 45). The vascular effects of ET-1 are mediated by ET_A and ET_B receptor subtypes (4, 52, 61). The ET_A receptor, located on vascular smooth muscle cells, causes vasoconstriction, whereas the ET_B receptor, located on vascular endothelial cells, results in vasodilation through the release of endothelium-derived mediators such as nitric oxide and prostacyclin (35, 68). ET_B receptors are also present on vascular smooth muscle cells and mediate vasoconstriction (33), although their relative contribution to ET-induced vasoconstriction remains ill defined.

ET-1 concentrations are increased in animal models of monocrotaline-induced pulmonary hypertension (25, 55), endotoxin-induced pulmonary hypertension (70), and pulmonary hypertension related to left heart failure (60). Notably, ET-1 immunoreactivity and ET mRNA expression are increased in plasma and lung specimens of patients with pulmonary hypertension (11, 16, 20, 27, 54, 64). Thus ET-1 has been implicated as a potential mediator of pulmonary hypertension.

Hypoxia is an important physiological stimulus for pulmonary vasoconstriction. Plasma ET-1 levels are elevated in subjects exposed to high altitudes and are directly proportional to pulmonary artery pressure and inversely related to arterial PO2 (28, 62). In animals, both nonselective ET-1 receptor blockade (21, 24, 37, 71) and specific ET_A antagonism have been shown to attenuate hypoxia-induced pulmonary hypertension (14, 21, 24, 30, 42, 56), whereas specific ET_B antagonism has minimal effect on pulmonary artery pressure (PAP) (24, 38). However, the role of ET-1 in human hypoxic pulmonary vasoconstriction remains to be studied.

We hypothesized that ET-1 contributes to the maintenance of basal systemic and pulmonary vascular tone in humans and that hypoxic pulmonary vasoconstriction is mediated in part by the increased activity of ET-1. Accordingly, we investigated the effect of D-Trp-D-Asp-Pro-D-Val-Leu (BQ-123), a selective ET_A receptor antagonist (41), on resting hemodynamics and on the hemodynamic response to acute hypoxia in healthy human volunteers.

METHODS

Study population. Participants in this study included 19 healthy volunteers who were recruited from the local com-
munity via newspaper advertisements. Eleven volunteers (seven men and four women, age 31 ± 4 yr) were enrolled in the experimental arm, and nine volunteers (four men and five women, age 26 ± 6 yr) served as controls. One subject was common to both groups. All of the subjects had a normal medical history and physical examination. Fasting glucose, blood urea nitrogen, creatinine, complete blood count, and fasting lipid profile were all within normal limits. No subject had diabetes mellitus, obesity, hypertension, dyslipidemia, or any clinical evidence of cardiac, pulmonary, renal, hepatic, or hematological abnormalities. All subjects denied a history of cigarette smoking, but one subject was retrospectively discovered to be a smoker. All subjects gave written, informed, and voluntary consent. The Human Research Committee of Brigham and Women's Hospital approved the study.

Hemodynamic measurements. Each subject was studied in a quiet, 23°C temperature-controlled room in the fasting state. Caffeine, alcohol, aspirin, and nonsteroidal inflammatory agents were prohibited within 48 h of the study. Under local anesthesia and sterile conditions, a 20-gauge polyethylene catheter was inserted into the left radial artery of each subject to measure mean systemic arterial pressure (MAP) and to obtain arterial blood gas and plasma samples. An 8.5-Fr sheath (Cordis, Miami, FL) was placed percutaneously into the right internal jugular vein. An 8-Fr, 5-lumen thermodilution catheter (Abbott Critical Care Systems, North Chicago, IL) was then advanced under continuous pressure monitoring into the pulmonary artery to measure pulmonary capillary wedge pressure (PCWP), PAP, and right atrial pressure (RAP). All pressures were recorded in the supine position with pressure transducers (Gould, Oxnard, CA; or Abbott Critical Care Systems) calibrated against a saline manometer positioned at the midsternal level and zeroed against atmospheric pressure. Measurements were recorded using a Gould 4600 Physiologic Recorder (Gould) or a Marquette Transcope 12C System (Gems I. T.; Milwaukee, WI). Heart rate (HR) was obtained from the electrocardiogram. Cardiac output (CO) was measured by thermodilution using 10-ml boluses of room temperature-normal saline as the injectate. At least five cardiac output measurements were made at each time point. The highest and lowest measurements were eliminated, and the remaining results were averaged. Systemic vascular resistance (SVR; in dyn·s·cm⁻⁵) was calculated as [MAP – RAP/CO] × 80 and pulmonary vascular resistance (PVR; in dyn·s·cm⁻⁵) was calculated as [(PAP – PCWP)/CO] × 80.

Induction of hypoxia. Hypoxia was induced by a protocol previously utilized and validated in our laboratory (6). Study subjects breathed a nitrogen-oxygen mixture via an air-oxygen blender (Puritan Bennett; Lawrenceville, GA) with nitrogen connected to the air inlet and wall source oxygen to the oxygen inlet of the blender. By changing the proportion of the two gases through the blender, the fraction of inspired oxygen (FIO₂) delivered to the study participant was precisely regulated. The blender was connected to a gas-powered demand valve in series with a nonrebreathing valve (Diemolding Healthcare Division; Canasta, NY). The subject breathed through a sealed facemask (Ventlab; Mocksville, NC).

Real-time measurements of the inspired oxygen content were made using a digital oxygen monitor (Catalyst Research; Owings Mills, MD) attached to the inlet of the nonrebreathing valve. Blood oxygen saturation was approximated by finger probe oximetry and confirmed by arterial blood gas analysis. Basal FIO₂ was 21% oxygen. A FIO₂ of between 10.8% and 17.2% was required to create hypoxic conditions approximating an arterial PO₂ of 50 mmHg, corresponding to an oxygen saturation of 84%.

Experimental protocol. All subjects rested for 30 min after the insertion of catheters to establish a stable baseline before data collection. The research laboratory was kept quiet and the lights were dimmed. Baseline hemodynamic measurements were initially taken with the subject breathing a FIO₂ of 21% (normoxic conditions) for ~30 min. Thereafter, hypoxia was induced to reduce the PO₂ to ~50 mmHg, and this was maintained for a period of 15 min. This period was sufficient to establish a steady state without causing discomfort to subjects from a more prolonged hypoxic exposure. Hemodynamic measurements and blood gas analyses were then repeated. The subject breathed a FIO₂ of 21% for at least 15 min to reestablish baseline oxygen saturation and hemodynamic indexes. Next, normal saline or the ETA receptor antagonist BQ-123 (Clinalfa; Lauelfingen, Switzerland) was administered via the right atrial catheter port at a rate of 0.4 ml/min or 200 nmol/min. This dose of BQ-123 was chosen to produce steady-state plasma concentrations 10-fold higher than the IC₅₀ for the ETA receptor and 10-fold lower than the IC₅₀ of BQ-123 for the ETB receptor (40). After 60 min of normal saline or BQ-123 administration, hemodynamic measurements were made under normoxic conditions. The hypoxic challenge was then repeated with measurements of the hemodynamic response and blood gas analysis. ET-1 levels were drawn from the arterial catheter at the completion of the initial baseline data collection, at the end of the first hypoxic challenge, and again after 60 min of BQ-123 infusion.

Measurement of ET. Samples for ET-1 levels were immediately placed on ice and then centrifuged. The plasma was then quick-frozen and stored at −70°C. ET-1 concentrations were measured by a commercially available ELISA (Bio-medicus; Vienna, Austria).

Statistical analysis. Values are expressed as means ± SE. Mean change (absolute and percent) in hemodynamic parameters was calculated by averaging the change for each individual. The effect of BQ-123 and hypoxia on pulmonary and systemic hemodynamic measurements was evaluated using a two-way ANOVA with repeated measures. Arterial blood gas analyses were compared using two-tailed paired t-tests. Statistical significance was accepted at the 95% confidence level (P < 0.05).

RESULTS

Effects of ET₄ receptor blockade on the pulmonary vascular bed during normoxia. ET₄ receptor antagonism with BQ-123 reduced normoxic PVR by 26 ± 8% (P = 0.02) (Fig. 1). CO increased by 22 ± 2% (P < 0.001), whereas SVR and MAP fell 22 ± 2% (P < 0.001) and 5 ± 2% (P = 0.03), respectively (Table 1). PAP, RAP, PCWP, and HR did not change [all P = not significant (NS)] (Table 1). During BQ-123 infusion, plasma ET-1 levels did not change (from 4.7 ± 1.0 to 4.7 ± 1.3 pg/ml, P = 0.67).

Effects of acute hypoxia on pulmonary vascular tone. In the experimental group, the hypoxic stimulus decreased PO₂ from 99.8 ± 1.8 to 49.4 ± 0.4 mmHg (P < 0.001); oxygen saturation fell from 98.2 ± 0.2% to 84.1 ± 0.2% (P < 0.001). Arterial pH and PCO₂ did not change, indicating that the acute hypoxic stimulus did not result in hyperventilation in these healthy subjects (Table 2).

During vehicle administration in the experimental group, acute hypoxia induced a 95 ± 17% increase in PVR (P < 0.001). This reflected a 61 ± 12% increase in
mean PAP (P < 0.001) and a 28 ± 4% rise in CO (P < 0.0001) (Table 1). MAP fell 3 ± 2% (P = 0.03) and SVR decreased 23 ± 3% (P < 0.0001), whereas RAP and PCWP did not change (both P = NS) (Table 1). HR increased 13 ± 4% (P < 0.0001) (Table 1). Plasma ET-1 levels did not change significantly (from 4.7 ± 1.0 to 5.2 ± 1.2 pg/ml, P = 0.14).

Effects of ETA receptor blockade on the hemodynamic response to hypoxia. Hypoxia, in the presence of BQ-123, increased PVR by 97 ± 17% compared with the value obtained under normoxic conditions after 60 min of BQ-123 infusion (P = 0.0003) (Table 1). Although the absolute increase in PVR was modestly blunted (55 ± 9 vs. 40 ± 7 dyn·s·cm⁻¹, P = 0.046), the 97% increase in PVR was comparable to the 95% increase that occurred during hypoxia in the absence of BQ-123 (P = 0.93) (Fig. 2). Stated differently, for a given value of baseline PVR, the incremental increase in PVR was the same under hypoxic conditions with or without BQ-123. Thus these results suggest that, although BQ-123 decreased the absolute PVR induced by hypoxia, its effect was largely derived from a reduction in resting PVR under normoxic conditions rather than an attenuation in the pulmonary vasoconstrictive response to hypoxia.

The overall hemodynamic response to hypoxia was similar during vehicle and BQ-123 infusion (Fig. 2). During BQ-123 infusion, mean PAP increased by 62 ± 13% (P < 0.001), whereas CO increased by 29 ± 5% (P = 0.0002). RAP, PCWP, and MAP did not change, whereas SVR fell by 22 ± 4% (P < 0.0001) (Table 1). HR increased significantly by 17 ± 4% (P < 0.0001) (Table 1).

Effect of repeated hypoxia on pulmonary vascular tone. To ascertain the effect of repeated hypoxia on PVR, a control group of nine patients was subjected to two sequential hypoxic exposures without ETA antagonism. Oxygen saturation decreased from 98.2 ± 0.4% to 83.1 ± 0.6% with the first hypoxic exposure and from 98.8 ± 0.3% to 85.2 ± 0.8% with the second hypoxic exposure.

The primary hypoxic challenge raised PVR by 44 ± 7 dyn·s·cm⁻⁵ or 77 ± 9% (P < 0.001), reflecting a 22 ± 7% increase in mean PAP (P = 0.02) and a 29 ± 4% increase in CO (P < 0.001) (Table 3). The second hypoxic exposure increased PVR by 56 ± 10

### Table 1. Effect of hypoxia on hemodynamic parameters during vehicle and BQ-123 infusions

<table>
<thead>
<tr>
<th></th>
<th>Normoxia/Vehicle</th>
<th>Hypoxia/Vehicle</th>
<th>Normoxia/Vehicle</th>
<th>Normoxia/BQ-123</th>
<th>Hypoxia/BQ-123</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVR, dyn·s·cm⁻⁵</td>
<td>64 ± 5</td>
<td>119 ± 10</td>
<td>67 ± 5</td>
<td>46 ± 5</td>
<td>85 ± 9</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>10 ± 1</td>
<td>15 ± 1</td>
<td>10 ± 1</td>
<td>9 ± 1</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>SVR, dyn·s·cm⁻⁵</td>
<td>1,368 ± 52</td>
<td>1,050 ± 57</td>
<td>1,351 ± 44</td>
<td>1,069 ± 38</td>
<td>828 ± 43</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>90 ± 4</td>
<td>86 ± 4</td>
<td>88 ± 3</td>
<td>85 ± 3</td>
<td>84 ± 3</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>5.3 ± 0.3</td>
<td>6.7 ± 0.4</td>
<td>5.2 ± 0.3</td>
<td>6.4 ± 0.3</td>
<td>8.3 ± 0.6</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>65 ± 2</td>
<td>74 ± 3</td>
<td>66 ± 2</td>
<td>70 ± 2</td>
<td>84 ± 22</td>
</tr>
</tbody>
</table>

Values are means ± SE. PVR, pulmonary vascular resistance; PAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SVR, systemic vascular resistance; MAP, mean systemic arterial pressure; CO, cardiac output; HR, heart rate. *P < 0.05, hypoxia/vehicle vs. normoxia/vehicle; †P < 0.05, normoxia/BQ-123 vs. normoxia/vehicle; ‡P < 0.001, hypoxia/BQ-123 vs. normoxia/BQ-123; §P < 0.01 hypoxia/BQ-123 vs. hypoxia/vehicle.
Both nonselective ETA/ETB and selective ETA receptor antagonists have been shown to decrease PVR in patients with heart failure (23, 43). High levels of ET-1 immunoreactivity and ET-1 mRNA have been found in pulmonary arterial endothelial cells of patients with plexogenic pulmonary arteriopathy (27). Chronic use of the nonselective ETA/ETB receptor antagonist bosentan has been demonstrated to reduce PVR and improve symptoms in patients with primary and scleroderma-induced pulmonary hypertension (13). The importance of ET in these pathological conditions in humans may be better understood as we examine the contribution of ET to the regulation of pulmonary vascular tone under physiological conditions.

**ET and the physiological regulation of vascular tone.** ET-1 administration in intact organisms, including humans, produces a biphasic hemodynamic response: a transient vasodilation, best observed at lower ET-1 concentrations, followed by sustained vasoconstriction (12, 55, 67, 70). Intrabrachial artery infusion of ET-1 increases forearm vascular resistance in humans (1, 15, 34), and systemic infusion of ET-1 increases SVR and MAP, with a concomitant decrease in CO and stroke volume (2, 3, 44). ET-1 administration also causes constriction of epicardial arteries and coronary arterioles (58). Studies in vitro suggest that ET-1-induced constriction is mediated primarily by the ETA receptor (56).

Several studies have assessed the contribution of ET to systemic vascular tone in healthy humans. Intra-arterial infusion of an ETA receptor antagonist reduced forearm vascular resistance in some studies (6, 23, 34, 68) but not in others (12). Local and systemic administration of BQ-788, an ETB antagonist, caused vasoconstriction (12, 65, 68), suggesting that the balance of effects of endogenous ET-1 on the ETB receptor favors vasodilation. Systemic administration of a nonselective ETAB receptor antagonist TAK-044 decreased mean arterial pressure and total peripheral resistance, determined noninvasively by bioimpedance, in healthy subjects (32). Our results, showing decreased SVR with systemic infusion of BQ-123, support the notion that ET contributes to basal systemic vascular tone via the ETA receptor.

In vitro and in vivo animal studies indicate that ET induces pulmonary vasoconstriction (9, 10, 48) and that it mediates vascular smooth muscle cell proliferation (43). Both mitogenic and pulmonary vasoconstrictor effects are mediated by the ETA receptor in animals (9, 73). In healthy humans, systemic ET infusion leads to increased PVR (2, 44). No prior study has assessed the physiological role of endogenous ET in regulating pulmonary vascular tone in healthy humans. By infusing the ETA receptor antagonist BQ-123 systemically, we found that ET contributes to basal pulmonary vascular tone in healthy humans via the ETA receptor. This finding is at odds with observations in animals that have been exposed to both nonselective ET$_A$/ET$_B$ and selective ETA receptor antagonists under resting normoxic conditions (19, 72). However, in humans, it is believed that normal vascular tone is maintained via a balance of vasoconstricting and vasodilating factors. Several authors have shown that human endothelial and pulmonary artery smooth muscle cells release ET-1 under normoxic conditions (46, 49). Further research is needed to determine whether ET contributes to basal forepaw vascular tone in healthy humans.

**Fig. 2.** Percent change in hemodynamic parameters due to hypoxia during vehicle infusion and during BQ-123 infusion. There was no significant difference (NS) in the percent change between vehicle and BQ-123 infusion for PVR, mean PAP, SVR, and CO.

### Table 2. Effect of hypoxia on arterial blood gas parameters

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIO$_2$, %</td>
<td>21.0 ± 0.2</td>
<td>13.2 ± 0.4$^a$</td>
</tr>
<tr>
<td>PO$_2$, mmHg</td>
<td>99.8 ± 1.8</td>
<td>49.4 ± 0.4$^a$</td>
</tr>
<tr>
<td>O$_2$ saturation, %</td>
<td>98.2 ± 0.2</td>
<td>84.1 ± 0.2$^a$</td>
</tr>
<tr>
<td>PCO$_2$, mmHg</td>
<td>42.9 ± 0.6</td>
<td>41.0 ± 1.3</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.01</td>
<td>7.43 ± 0.01</td>
</tr>
</tbody>
</table>

Values are means ± SE. FIO$_2$, fraction of inspired oxygen. $^a$ P ≤ 0.01 vs. normoxia.
thermore, nitroprusside, a nitric oxide donor, has been shown to decrease basal ET-1 mRNA levels in human endothelial cells exposed to normoxia (46). These results, combined with our previous observation that acetylcholine decreases PVR in normoxic humans, suggest that unlike animals, the human pulmonary vasculature is not maximally dilated at rest and support our finding that ET-1 may be involved in maintaining optimal pulmonary vascular tone under resting conditions (17).

Role of ET-1 in hypoxic pulmonary vasoconstriction. Hypoxic pulmonary vasoconstriction was first reported in an animal model in 1946 by von Euler and Liljestrand (69) and in humans in 1947 by Motley et al. (53). Hypoxia is an important cause of pulmonary hypertension in diseases such as obstructive sleep apnea, sickle cell disease, and persistent pulmonary hypertension of the newborn. Our laboratory and others (8, 26) have shown previously that acute hypoxia causes peripheral vasodilation, pulmonary vasoconstriction, increased CO, and decreased mean arterial pressure. We have shown that nitric oxide serves as a counterregulatory mechanism for hypoxic pulmonary vasoconstriction, and yet the mechanism of the vasoconstriction itself remains ill defined (8). Animal models indicate that chronic hypoxia results in increased plasma ET-1 immunoreactivity and ETA and ETB receptor expression (22, 47). In several animal models of chronic hypoxia, ETA or combined ETA/ETB receptor antagonists prevent or attenuate hypoxia-induced increases in PAP and suppress vascular remodeling and progression of right ventricular hypertrophy (9, 14, 18, 21, 24, 29, 30, 39, 56, 63). ETB antagonism alone has little effect on chronic hypoxic pulmonary hypertension (24, 38). There are conflicting reports, however, regarding the role of ET-1 in the pulmonary vascular response to acute hypoxia. Evidence supporting a role for ET-1 has been reported in dogs who were made acutely hypoxic in the presence and absence of BQ-485, an ETA selective receptor antagonist, as well as bosentan (19). Conversely, data disputing the contribution of ET-1 have been reported in dogs who were made acutely hypoxic with and without BQ-123 (66, 72). Our data indicates that ETA receptor blockade in humans does not prevent the vasoconstrictive response induced by acute hypoxia, beyond its effect on lowering basal pulmonary vascular tone. The absence of an increase in plasma ET-1 levels is consistent with the contention that ET does not contribute to pulmonary vasoconstriction during acute hypoxia. Furthermore, the lack of increase in plasma ET-1 levels suggest that BQ-123 selectively blocked ETA receptors and did not displace ET-1 from ETB receptors.

Potential limitations. One of the shortcomings inherent in human experimentation is the inability to measure PVR by constructing a multipoint plot relating the transpulmonary gradient to CO. Our results are therefore susceptible to the errors introduced by the calculation of PVR from single point measurements of pressure-flow ratios (50).

A limitation of this study is that we were unable in one experimental setting to administer both vehicle and BQ-123, due to its long half-life, in a randomized fashion. This raises the concern that the effect of BQ-123 may have been underestimated if repetitive exposures to hypoxia result in progressive increases in PVR. Studies in dogs have suggested that the hypoxic pulmonary vasoconstrictive response is potentiated by repeated exposures to hypoxia (5, 59, 67). However, the only human study evaluating the pulmonary vascular response to repetitive hypoxia did not show any augmentation of the pulmonary vasoconstrictive response with three consecutive hypoxic exposures (7). Our data in the control population suggest a trend toward increased vasoconstriction with repeated hypoxia, but the difference did not reach statistical significance. Thus we believe that it is unlikely that the effects of ETA receptor blockade were underestimated in this study because of nonrandom BQ-123 administration.

Another potential shortcoming of this study was that time and patient safety concerns did not permit us to conduct a dose-response curve to assess the effect of variable doses of BQ-123 on hypoxic pulmonary vasoconstriction. Dose-dependency studies looking at the effect of intra-arterial BQ-123 on forearm blood flow demonstrated that maximal vasodilation was achieved at a dose of 50 nmol/min (6). The BQ-123 dose of 200 nmol/min utilized in our study far exceeds the dose required to produce maximal vasodilation. Therefore, it is unlikely that the contribution of ET-1 to hypoxic pulmonary vasoconstriction was underestimated secondary to inadequate ETA receptor blockade.

The role of ET-1 in hypoxic pulmonary vasoconstriction and in primary and secondary pulmonary hyper-

Table 3. Effect of repeated hypoxia on hemodynamic parameters during repeated vehicle infusion

<table>
<thead>
<tr>
<th>Normoxia 1/Vehicle</th>
<th>Hypoxia 1/Vehicle</th>
<th>Normoxia 2/Vehicle</th>
<th>Hypoxia 2/Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVR, dyn·s·cm⁻⁵</td>
<td>61 ± 8</td>
<td>105 ± 12*</td>
<td>56 ± 9</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>19 ± 1</td>
<td>23 ± 2*</td>
<td>17 ± 1</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>15 ± 1</td>
<td>14 ± 1</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>RAP, mmHg</td>
<td>10 ± 1</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>SVR, dyn·s·cm⁻⁵</td>
<td>1,186 ± 82</td>
<td>943 ± 75*</td>
<td>1,115 ± 64</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>92 ± 3</td>
<td>93 ± 2</td>
<td>93 ± 2</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>5.7 ± 0.4</td>
<td>7.4 ± 0.6*</td>
<td>6.2 ± 0.3</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>57 ± 3</td>
<td>70 ± 4*</td>
<td>62 ± 4</td>
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</table>

Values are means ± SE. *P < 0.05, hypoxia 1/vehicle vs. normoxia 1/vehicle; †P < 0.01, hypoxia 2/vehicle vs. normoxia 2/vehicle. All P = not significant (NS) for normoxia 2/vehicle vs. normoxia 1/vehicle; All P = NS for hypoxia 2/vehicle vs. hypoxia 1/vehicle.
tension may be affected by the duration of the hypoxic stimulus. Our findings assess the contribution of ET-1 to acute hypoxic pulmonary vasoconstriction. We cannot discount the possibility that ET-1 may contribute to pulmonary tone during chronic hypoxia that underlies many pathological forms of pulmonary hypertension. Furthermore, ET-1 might only be involved in mediating the pulmonary vascular response to acute hypoxia at arterial Po2 concentrations <50 mmHg. Once again, time and safety considerations did not allow us to assess the response to BQ-123 at different oxygen concentrations. Nonetheless, at an arterial Po2 of 50 mmHg, well within the range of tensions seen clinically, other mechanisms as yet undefined must account for the increase in PVR that occurs in humans during acute exposure to hypoxic conditions.

In conclusion, the data presented here contribute importantly to our understanding of the physiological regulation of vasomotor tone in humans. We found that ET, via the ETA receptor, constitutively constricts the pulmonary vascular bed in healthy individuals. However, acute hypoxic pulmonary vasoconstriction is not primarily mediated by ET beyond its effects on basal tone.

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