Published in final edited form as:

Respir Physiol Neurobiol. 2011 July 31; 177(2): 98–107. doi:10.1016/j.resp.2011.04.005.

Pulmonary capillary recruitment in response to hypoxia in healthy humans: a possible role for hypoxic pulmonary venoconstriction?

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Abstract

We examined mechanisms by which hypoxia may elicit pulmonary capillary recruitment in humans. On separate occasions, twenty-five healthy adults underwent exposure to intravenous saline infusion (30 ml/kg ~15min) or 17-h normobaric hypoxia ($F_{iO_2}=12.5\%$). Cardiac output ($\dot{Q}$) and pulmonary capillary blood volume (V_c) were measured before and after saline infusion and hypoxic-exposure by a rebreathing method. Pulmonary artery systolic pressure (sPpa) and left ventricular (LV) diastolic function were assessed before and after hypoxic-exposure via echocardiography. Saline infusion increased $\dot{Q}$ and V_c ($P<0.05$) with no change in $V_c/\dot{Q}$ ($P=0.97$). Hypoxic-exposure increased V_c ($P<0.01$) despite no change in $\dot{Q}$ ($P=0.25$), increased sPpa ($P<0.01$), and impaired LV relaxation. Multiple regression suggested that ~37% of the hypoxia-mediated increase in V_c was attributable to alterations in $\dot{Q}$, sPpa and LV diastolic function. In conclusion, hypoxia-induced pulmonary capillary recruitment in humans is only partly accounted for by changes in $\dot{Q}$, sPpa and LV diastolic function. We speculate that hypoxic pulmonary venoconstriction may play a role in such recruitment.

Keywords

Hypoxic pulmonary vasoconstriction; pulmonary capillary blood volume; cardiac output; pulmonary artery pressure; left ventricular diastolic function

1. Introduction

Airway hypoxia elicits recruitment of the pulmonary capillaries with a concomitant increase in the total surface area for gas exchange and lung diffusing capacity (Wagner et al. 1975; Wagner et al. 1979; Capen et al. 1982; Brimiouille et al. 1996). Theoretically, hypoxia-

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induced recruitment of the pulmonary capillaries may be attributable to increases in cardiac output ($\dot{Q}$), left atrial (LA) pressure, pressure within the post-capillary vessels (i.e. the pulmonary vein and venules), pressure within the pre-capillary vessels (i.e. the pulmonary artery and arterioles), or a combination of the aforementioned factors. While an elevated $\dot{Q}$ would cause pulmonary capillary recruitment through passive distension of the pulmonary circulation, an increase in LA pressure would facilitate recruitment of the pulmonary capillaries through a retrograde rise in pulmonary capillary pressure (Ppc) (Wagner and Latham, 1975; Wagner et al., 1975). Similarly, hypoxia-induced constriction of post-capillary pulmonary vessels would increase pressure downstream of the pulmonary capillaries with a subsequent rise in Ppc and pulmonary capillary recruitment, whereas a general constriction of the pre-capillary pulmonary vessels may increase pulmonary artery pressure (Ppa) sufficiently to overcome the normally existing perfusion gradient imposed by gravity increasing pulmonary capillary recruitment secondary to a redistribution of blood flow to the upper segments of the lung (Wagner et al. 1975; Wagner et al. 1979). However, it has been shown previously that hypoxia-induced recruitment of the pulmonary capillaries is largely independent of alterations in $\dot{Q}$ and LA pressure in the dog lung (Wagner et al. 1975; Wagner et al. 1979). In addition, while hypoxia has been shown to elicit constriction of the post-capillary as well as the pre-capillary pulmonary vessels in both human and animal models (e.g., Wagner et al. 1979; Hoshino et al. 1988; Sheehan et al. 1992; Zhao et al. 1993; Hillier et al. 1997; Maggiorini et al. 2001), the magnitude of hypoxia-induced pulmonary capillary recruitment in the dog lung correlates well with Ppa but not pulmonary vein pressure (Ppv) (Wagner et al. 1979). Moreover, Wagner et al. (1979) demonstrated that infusion of the vasodilator prostaglandin E₁ reversed the pulmonary capillary recruitment associated with airway hypoxia with a corresponding reduction in Ppa but no change in Ppv. Based on the aforementioned considerations, it is likely that hypoxia-induced recruitment of the pulmonary capillaries in the dog lung is mediated primarily by an increase in Ppa secondary to constriction of the pre-capillary pulmonary vessels rather than alterations in $\dot{Q}$ and LA pressure, or constriction of the post-capillary pulmonary vessels.

In a more recent study designed primarily to assess the influence of hypoxia on lung fluid balance, we observed that pulmonary capillary blood volume (V_c) was increased after 17-h hypoxic exposure relative to baseline values, indicating that hypoxia elicits pulmonary capillary recruitment in healthy humans (Snyder et al. 2006). Additionally, we and others have shown that hypoxia is associated with mild left ventricular (LV) diastolic dysfunction, which would be expected to increase LV and LA pressure (Allemann et al. 2004; Kjaergaard et al. 2006; Pham et al. 2010), and there is evidence that the post- as well as the pre-capillary pulmonary vessels undergo constriction in response to hypoxic exposure in humans (Hoshino et al. 1988; Maggiorini et al. 2001). However, how these mechanisms interact to mediate hypoxia-induced recruitment of the pulmonary capillaries in humans remains unclear. Accordingly, through retrospective analysis of data previously collected and published from our laboratory (Kjaergaard et al. 2006; Snyder et al. 2006), we aimed to explore the potential mechanisms by which hypoxia may elicit an increase in pulmonary capillary blood volume in healthy humans. Addressing this aim is important not only to elucidate the mechanisms that underpin the pulmonary capillary recruitment associated with hypoxia, but may also help resolve some of the controversy in the literature over whether hypoxic pulmonary vasoconstriction occurs in the post-capillary as well as the pre-capillary vessels in healthy humans.

2. Materials and Methods

2.1. Subjects

Twenty-five healthy, non-smoking subjects (18 male, 7 female) participated in the study [means $\pm$ SEM (range): age = 31 ± 2 (21 - 45) years, stature = 176 ± 2 (155 - 194) cm, body

mass = 78 ± 3 (50 - 97) kg, BMI = 25 ± 1 (19 - 34) kg/m²]. Data pertaining to 18 of the 25 subjects and 14 of the 17 subjects assessed by Snyder et al. (2006) and Kjaergaard et al. (2006), respectively, are present within the current study. Cardiac output and pulmonary capillary blood volume data for 7 subjects in the present study are previously unpublished. All subjects were free from cardiovascular and lung disease and had pulmonary function within normal limits (Table 1). The experimental procedures were approved by the Mayo Clinic Institutional Review Board and each subject provided written informed consent prior to participation.

2.2. Experimental Procedures

The experimental procedures were conducted during two laboratory sessions that were separated by at least 48 h but not longer than 4 days (Fig. 1). The subjects abstained from caffeine for 12 h and exercise for 48 h before each session. During the first session, pulmonary function was assessed according to standard procedures (Miller et al. 2005) before the subjects underwent rapid intravenous saline infusion (30 ml/kg over ~ 15 min). At the second visit, the subjects were exposed to 17-h of normobaric hypoxia ($F_{I_{O_2}} = 12.5\%$, barometric pressure = 732 mmHg) in a hypoxic tent. Cardiac output ($\dot{Q}$) and pulmonary capillary blood volume (V_c) were assessed before and after saline infusion and hypoxic exposure by measuring the disappearance of small amounts of acetylene (C_2H_2), carbon monoxide (CO), and nitric oxide (NO) during a rebreathe technique. In addition, echocardiographically derived measures of $\dot{Q}$, pulmonary artery systolic pressure (sPpa) and left ventricular diastolic function were made before and immediately after hypoxic exposure (Fig. 1).

2.3. Pulmonary Capillary Blood Volume and Cardiac Output via rebreathe

V_c and $\dot{Q}$ were assessed using a rebreathe technique, as described previously (Snyder et al. 2006; Ceridon et al. 2010). Gas concentrations were sampled continuously during each rebreathe maneuver with a mass spectrometer and a NO analyzer, which were integrated with custom analysis software for the determination of V_c and $\dot{Q}$. Following each maneuver, the rebreathe bag was emptied with a vacuum pump before being refilled for the next maneuver. Rebreathes derived measures of V_c and $\dot{Q}$ were made in triplicate before and after saline infusion and hypoxic exposure.

2.3.1. Pulmonary capillary blood volume—Previously, measurement of V_c required assessing the disappearance of carbon monoxide (CO) in the presence of at least two, preferably three, different oxygen tensions. More recently, however, Tamhane et al. (2001) showed that V_c could be assessed accurately by simultaneously measuring the disappearance of nitric oxide (NO) and CO at one oxygen tension only. We have since used this technique to determine V_c under both normoxic and hypoxic conditions (Snyder et al. 2006; Ceridon et al. 2010). In the present study, diffusing capacity of the lungs for CO and NO (DLCO and DLNO, respectively), were assessed with subjects in the upright position. The subjects breathed through a two-way switching valve (Hans Rudolph 4285 series, Hans Rudolph, Kansas City, MO) that was connected to a pneumotachometer (MedGraphics preVent Pneumotach, Medical Graphics Corporation, St. Paul, MN), a mass spectrometer (Marquette 1100 Medical Gas Analyzer, Perkin-Elmer, St. Louis, MO) and a NO analyzer (Sievers 280i NOA, Sievers, Boulder, CO). The inspiratory port of the switching valve was set to either room air or a 5-liter anesthesia bag that was filled with 0.3% CO ($C^{18}O$), 40 parts per million (ppm) NO (diluted in the bag immediately before the rebreathe maneuver from an 800 ppm gas mixture), O_2 (35% for rapid saline infusion visit, 18% for hypoxic exposure visit), and N_2 balance. $C^{18}O$ was used instead of the more common $C^{16}O$ as the mass spectrometer cannot distinguish $C^{16}O$ from N_2 . The total volume of gas in the anesthesia bag was determined by the resting tidal volume of each subject. To ensure the

volume of the test gas was consistent across multiple rebreathe maneuvers, the bag was filled using a timed switching circuit, which, given a consistent flow rate from the tank, resulted in the desired volume. The test gas volume given by the switching circuit was verified prior to the pre- and post-saline and hypoxic exposure rebreathe maneuvers using a 3 liter syringe. Prior to each maneuver, the subjects were instructed to breathe normally on room air for 4 to 5 breaths. At the end of a normal expiration (i.e. at functional residual capacity), the subjects were switched into the rebreathe bag and told to nearly empty the bag with each breath for 10 consecutive breaths. The subjects maintained respiratory frequency at $32 \text{ breaths} \cdot \text{min}^{-1}$ during each maneuver by following a metronome with distinct inspiratory and expiratory tones. The respiratory frequency was set at $32 \text{ breaths} \cdot \text{min}^{-1}$ so that data could be collected over 8-10 breaths before the NO in the test gas decayed completely. For the pre-hypoxia measures, the subject's alveolar O_2 was allowed to equilibrate to the low O_2 used in the test gas by having them pre-breathe 12.5% O_2 for 10 to 12 breaths before switching them into the rebreathe bag. This allowed us to more accurately compare the before and after hypoxic exposure measures of V_c . Importantly, our pre-saline infusion and pre-hypoxic exposure measures of V_c were not different ($86 \pm 7 \text{ ml}$ vs. $84 \pm 8 \text{ ml}$, $P = 0.885$). That is, having the subjects transiently pre-breathe the low O_2 gas mixture had little or no effect on pulmonary capillary recruitment prior to our pre-hypoxia measure of V_c . In addition, it should be noted that with our technique, the 40 ppm NO concentration dilutes to $<20 \text{ ppm}$ on the first inhalation and rapidly declines to undetectable values typically within 8 breaths. Thus, it is unlikely that the concentration of NO used in the test gas was large enough to have a vasoactive effect itself.

2.3.2. Cardiac output— $\dot{Q}$ was measured using a validated 8- to 10-breath acetylene rebreathe technique using the same anesthesia bag containing the diffusion gas mixtures with the addition of 0.7% C_2H_2 and 9% He (Johnson et al. 2000; Bell et al. 2003).

2.4. Cardiac Output, Pulmonary Artery Pressure and Left Ventricular Diastolic Function via echocardiography

$\dot{Q}$, pulmonary artery systolic pressure (sPpa) and left ventricular (LV) diastolic function were measured before and immediately after hypoxic exposure by echocardiographic examination (Vivid 7, GE Healthcare, Milwaukee, WI, USA). All images were captured by the same sonographer throughout the study, and were stored and analyzed off-line by the same experimenter using commercially available software (GE EchoPac® software, version 4.0).

2.4.1. Cardiac output—As a second measure of $\dot{Q}$ in response to hypoxic exposure, stroke volume (SV) was estimated in 14 subjects as LV outflow velocity time integral multiplied by the end-systolic LV outflow tract diameter according to standard procedures (Quinones et al. 2002). $\dot{Q}$ was subsequently calculated as the product of SV and heart rate (f_H).

2.4.2. Pulmonary artery pressure—sPpa was estimated from the peak velocity of tricuspid regurgitation (TR) using a modified Bernoulli equation, as described previously (Yock et al. 1984; Quinones et al. 2002). Briefly, with subjects in the left lateral supine position, the TR jet was located using 2D-colour Doppler echocardiography. Agitated saline was injected intravenously as needed to enhance the Doppler signal of TR. The maximal velocity of the TR jet was determined by careful application of the continuous wave sampler within and parallel to the regurgitation jet and sPpa was computed as $4\text{TR}^2 + \text{right atrial pressure}$, which was presumed to be 5 mmHg.

2.4.3. Left ventricular function—Echocardiographic determination of LV diastolic function was performed in 14 subjects in the left lateral supine position. The primary measures of LV diastolic function made were: 1) early (E) and late (A) transmitral flow velocities and the ratio of early to late peak velocities (E/A) by pulsed wave Doppler, 2) peak early (e') and late (a') septal mitral annular velocities and the ratio of early to late myocardial relaxation velocities (e'/a') by pulsed wave tissue Doppler, and 3) isovolumetric relation time (IVRT), defined as the interval from the closure of the aortic valve to the opening of the mitral valve, by Doppler echocardiography.

2.5. Saline Infusion

To assure the sensitivity of our rebreathe technique for detecting changes in Vc, we used a rapid saline infusion to determine the effect of a passive rise in Q on our measure of Vc. On reporting to the laboratory, subjects lay supine and an 18-gauge venous catheter was inserted into a predominant antecubital vein. Subjects were moved to the upright position and baseline measures of Q and Vc (via rebreathe) were made. Saline was then infused intravenously (30 ml/kg over ~15 min) before repeat assessments of Q and Vc were made. Arterial oxygen saturation (SpO₂) and f_H were measured continuously during saline infusion using a pulse oximeter and finger sensor (Nellcor N-595, Tyco Healthcare Group, Nellcor Puritan Bennett Division, Pleasanton, CA).

2.6. Hypoxic Exposure

The subjects were exposed to normobaric (barometric pressure 732 mmHg) hypoxia for 17-h overnight in a specially designed tent with a controlled inspired oxygen concentration (F_IO₂ = 12.5%) (Colorado Altitude Training Corporation, Boulder, CO). Before entering the tent, pre-hypoxia measures of sPpa, Q, and Vc were made in every subject. In addition, LV diastolic function and Q (via echocardiography) were assessed in a subgroup of 14 subjects prior to entering the tent. While in the tent, SpO₂ and f_H were measured continuously using pulse oximetry (Nellcor N-595) and blood pressure was measured manually every two hours using a stethoscope and sphygmomanometer. Post-hypoxia measures of sPpa, LV diastolic function and Q (via echocardiography) were made in the hypoxic tent immediately after the completion of the 17-h hypoxic exposure. The subjects were then equipped with a tight fitting mask attached to a large gas reservoir that was connected to a portable gas tank of 12.5% O₂ and were transferred to the main physiology laboratory where repeat measures of Q and Vc (via rebreathe) were made with the subjects still in a hypoxic state.

2.7. Statistical Analyses

The within-subject coefficient of variation (CV) for Vc, Q, sPpa and indices LV diastolic function was used to estimate the sample size required to detect relatively small pre- to post-hypoxic exposure changes in these variables given a statistical power of 0.8 and an alpha level of 0.05 (Hopkins et al. 1999). Based on a CV of 5.1% for Vc, 6.2% for Q, 8.2% for sPpa, 4.7% for e' and 6.9% for IVRT (data from our laboratory), a sample size of 25 allowed us to detect a 4% change in Vc, a 5% change in Q and a 7% change in sPpa. In addition, a sample size of 14 allowed us to detect a 5% change in e' and a 7% change in IVRT. Paired samples t-test was used to compare absolute measurements of cardiac output and pulmonary capillary blood volume across time (pre-saline infusion vs. post-saline infusion, pre-hypoxia vs. post-hypoxia). Paired-samples t-test was used to compare pulmonary artery systolic pressure and indices of LV diastolic function pre- vs. post-hypoxia. Pearson's product-moment correlation coefficient (*r*) was computed to assess the relationship between pulmonary capillary blood volume and cardiac output, pulmonary artery systolic pressure, and indices of LV diastolic function (absolute values and the percent change from pre- to post-hypoxic exposure). In addition, multiple linear regression

analysis was used to examine the influence of cardiac output, pulmonary artery systolic pressure, and LV diastolic function on pulmonary capillary blood volume (absolute values and the percent change from pre- to post-hypoxic exposure). The acceptable type I error was set at $P < 0.05$. Results are expressed at means $\pm$ SEM. Statistical analyses were performed using SPSS version 12.0 for Windows (SPSS, Chicago, IL).

3. Results

3.1. Saline Infusion

Rapid saline infusion was associated with a $18 \pm 6\%$ increase in f_H (60 ± 9 vs. 72 ± 14 bpm, $P < 0.01$) but no change in SpO_2 (98 ± 1 vs. $98 \pm 1\%$). Saline infusion caused an increase in $\dot{Q}$ ($37 \pm 6\%$, $P < 0.01$) and V_c ($39 \pm 13\%$, $P = 0.02$) (Fig. 2). V_c corrected for $\dot{Q}$ was not different pre- vs. post-saline infusion ($P = 0.97$), suggesting that the increase in V_c observed with acute fluid loading was mediated primarily by an increase in $\dot{Q}$ (Fig. 2).

3.2. Hypoxic Exposure

Hypoxic exposure was associated with a significant and sustained decrease in SpO_2 , an increase in f_H , and no change in SBP, DBP or MAP (Table 2).

3.2.1. Pulmonary capillary blood volume and cardiac output via rebreath—

Hypoxic exposure was associated with an increase in V_c ($42 \pm 19\%$, $P = 0.03$) despite no change in $\dot{Q}$ ($P = 0.25$) (Fig. 2). Accordingly, V_c corrected for $\dot{Q}$ was greater post- vs. pre-hypoxic exposure ($P = 0.04$), suggesting that the hypoxia-induced increase in V_c was largely independent of a change in $\dot{Q}$ (Fig. 2).

3.2.2. Cardiac output, pulmonary artery pressure and left ventricular diastolic function via echocardiography—

The hypoxia-induced increase in f_H was accompanied by a significant reduction in echocardiographically derived SV (Table 2). Accordingly, in agreement with the rebreath estimate of $\dot{Q}$, there was no change in our echocardiographic estimate of $\dot{Q}$ from pre- to post-hypoxic exposure (Table 2). Individual subject and group mean changes in sPpa in response to hypoxic exposure are shown in Fig. 3. Immediately after hypoxic exposure, group mean sPpa was increased above pre-hypoxic exposure baseline values ($33 \pm 5\%$, $P < 0.01$). Moreover, all of the individual data points were greater post- vs. pre-hypoxic exposure, indicating that hypoxia induced an increase in sPpa in every subject. The changes in LV diastolic Doppler measurements associated with hypoxic exposure are shown in Table 2. Hypoxia did not change E ($P = 0.291$) but caused an increase in A ($P = 0.024$) with a corresponding decrease in the E/A ratio ($P = 0.036$). Individual subject and group mean changes in e' and IVRT from pre- to post-hypoxic exposure are shown in Fig. 3. Immediately after hypoxic exposure, group mean e' was decreased below baseline values ($19 \pm 3\%$, $P < 0.01$), as was the e'/a' ratio ($P = 0.017$). Conversely, group mean IVRT was increased post-hypoxia relative to baseline values ($160 \pm 61\%$, $P < 0.01$). These data indicate that hypoxic exposure induced a mild alteration in left ventricular relaxation in our subjects.

3.3. Correlations between Variables and Multiple Regression Analysis

The correlations between absolute values of V_c and $\dot{Q}$, sPpa, e' and IVRT measured before and after hypoxic exposure are shown in Fig. 4. There was a weak but significant relationship between V_c and $\dot{Q}$ ($r = 0.31$, $P = 0.028$) and between V_c and sPpa ($r = 0.30$, $P = 0.032$). By contrast, V_c was not significantly related with either e' or IVRT ($r = 0.38$, $P = 0.089$ and $r = 0.26$, $P = 0.168$, respectively). The correlations between the hypoxia-induced percent changes in V_c and the percent changes in $\dot{Q}$, sPpa, e' and IVRT are shown in Fig 5. The change in V_c did not correlate significantly with alterations in $\dot{Q}$ or the change in sPpa

($r = 0.09$, $P = 0.656$ and $r = 0.10$, $P = 0.681$, respectively). In addition, the change in Vc did not correlate with either the change in e' or the change in IVRT ($r = 0.23$, $P = 0.431$ and $r = 0.21$, $P = 0.477$). Multiple regression analysis suggested that ~37% of the hypoxia-induced increase in Vc was explained by the alterations in $\dot{Q}$, sPpa and e' (Table 3).

4. Discussion

4.1. Main Findings

The major findings of the present study were that 17-h exposure to normobaric hypoxia resulted in 1) an increase in pulmonary capillary blood volume (Vc) despite no change in cardiac output ($\dot{Q}$), 2) an increase in pulmonary artery systolic pressure (sPpa), and 3) impaired left ventricular relaxation as evidenced by a decrease in peak early septal mitral annular relaxation velocity (e') and an increase in isovolumetric relaxation time (IVRT). However, multiple regression analysis suggested that only ~37% of the hypoxia-mediated increase in Vc was explained by alterations in $\dot{Q}$, sPpa, e' . These findings suggest that mechanisms other than increases in cardiac output, pressure within the pre-capillary pulmonary vessels and left atrial pressure contribute to the pulmonary capillary recruitment associated with hypoxia in healthy humans.

4.2. Technical Considerations

4.2.1. Sensitivity of the rebreathe technique—The interpretation of our finding that hypoxic exposure elicits pulmonary capillary recruitment in healthy humans is critically dependent on the sensitivity of our rebreathe technique for detecting systematic within-day, between-occasion changes Vc. In the present study, we used a rapid intravenous saline infusion to determine the effect of a passive increase in $\dot{Q}$ on our measure of Vc. As anticipated, saline infusion was associated with a significant increase in $\dot{Q}$ (37%) with a concomitant increase in Vc (39%). Additionally, hypoxic exposure caused a 42% increase in Vc, with the likely range of the true effect of hypoxic exposure on Vc in the average subject (6% to 70%; 95% confidence interval) including changes more than 8-fold greater than the coefficient of variation for the measure of Vc in our laboratory (~5%). Therefore we are confident that the rebreathe technique used in the present study was sufficiently sensitive to detect changes in Vc. Accordingly, we believe that the pre- to post-hypoxic exposure increase in Vc represents a true effect of hypoxia on pulmonary capillary recruitment.

4.2.2. Echocardiographically derived measure of sPpa—One concern is that, due to its indirect nature, our echocardiographically derived estimate of sPpa may not provide an accurate representation of true pulmonary artery pressure. Indeed, if our echocardiographic assessment of TR velocity over- or underestimated sPpa, then it would perhaps be unsurprising that the hypoxia-induced change in Vc was largely independent of changes in sPpa in the present study. However, it has been shown previously that Doppler-derived gradients across the tricuspid valve correlate well with invasively measured pulmonary artery pressure at altitude (Allemann et al. 2004) as well as at sea level (Yock et al. 1984). For example, Yock and Popp (1984) demonstrated that sPpa estimated from TR velocity differed by less than 4 mmHg compared to direct measures of sPpa recorded from indwelling pulmonary artery catheters in 14 patients. In addition, Allemann et al. (2004) reported a strong positive correlation between echocardiographically derived and invasively measured sPpa ($r = 0.89$, $P = 0.0001$) in 28 subjects at altitude. Therefore, it appears that the Doppler derived estimates of sPpa based on TR velocity used in the present study provide an accurate measure of sPpa in normoxia and hypoxia.

4.3. Hypoxia-induced Pulmonary Capillary Recruitment: Potential Mechanisms

In the present study, hypoxic exposure was associated with recruitment of the pulmonary capillaries in healthy humans, as evidenced by an increase in pulmonary capillary blood volume. We hypothesized that the hypoxia-induced increase in Vc would be attributable to one or more of three primary mechanisms.

4.3.1. Hypoxia-induced alterations in $\dot{Q}$ —It is commonly held that short-term hypoxic exposure elicits an increase in resting $\dot{Q}$ secondary to a rise in heart rate that is mediated by concurrent sympatho-excitation and vagal withdrawal (Eckberg et al. 1982; Koller et al. 1988). Any such increase in $\dot{Q}$ in response to hypoxia would be expected to facilitate recruitment of the pulmonary capillaries through passive distension of the pulmonary circulation. However, the exact affect of short-term hypoxia on cardiovascular function at rest remains somewhat unclear, with some (Capen et al. 1982; Hanson et al. 1989; Dorrington et al. 1997; Maggiorini et al. 2001; Calbet et al. 2003) but not all (Fukuda et al. 2010; Pham et al. 2010; Wagner et al. 1975; Arai et al. 2009) previous studies reporting an elevation in $\dot{Q}$ in response to hypoxic exposure. For example, Hanson et al. (Hanson et al. 1989) demonstrated a ~30% increase in $\dot{Q}$ in response to 10 minutes of airway hypoxia in the dog lung. In addition, Maggiorini et al. (Maggiorini et al. 2001) reported that $\dot{Q}$ increased from $3.3 \pm 0.1 \text{ L}\cdot\text{min}^{-1}$ to $4.5 \pm 0.5 \text{ L}\cdot\text{min}^{-1}$ in 29 humans exposed to 10 minutes of alveolar hypoxia ($F_{\text{IO}_2} = 12\%$). By contrast, Wagner and Latham (Wagner et al. 1975) did not observe a significant change in $\dot{Q}$ in the dog in response to 15 minute periods of airway hypoxia of increasing severity. Moreover, Fukuda et al. (2010) evidenced no change in $\dot{Q}$ in response to 15 minutes of hypoxic exposure ($F_{\text{IO}_2} = 14.4\%$) in nine otherwise resting humans. While the divergence amongst the aforementioned findings regarding the affect of short-term hypoxic exposure on $\dot{Q}$ has not been systematically explored, likely explanations include variations in the severity of hypoxia induced, the species examined, and the methods used to determine changes in the cardiovascular parameters of interest. In humans, a further key determinant of this disparity appears to be the duration of the hypoxic exposure, with short exposures eliciting an increase in $\dot{Q}$ before trending back towards pre-hypoxia levels after ~24 hours. Interestingly, Dorrington et al. (Dorrington et al. 1997) demonstrated that hypoxia was associated with an abrupt and progressive increase in $\dot{Q}$ that tended to plateau between 6 and 8 hours of hypoxic exposure in seven healthy humans. In the present study, 17-h hypoxic exposure was associated with a 42% increase in Vc despite no change in either rebreathe or echocardiographically derived $\dot{Q}$. The maintenance in $\dot{Q}$ with hypoxia was the result of a significant reduction in stroke volume in the face of an increase in heart rate. In combination, these data suggest that the “break-point” at which $\dot{Q}$ begins to return to pre-hypoxia levels secondary to a reduction in stroke volume occurs between 8 and 17 hours of hypoxic exposure in humans. Presently, while there was a weak but significant relationship between absolute values of Vc and $\dot{Q}$ (Fig. 4), the pre- to post-hypoxia percent change in Vc was not related to the change in $\dot{Q}$ (Fig. 5). Moreover, multiple regression analysis suggested that ~29% of the pre- to post-hypoxia variance in Vc was explained by $\dot{Q}$ (Table 3). These data suggest that the hypoxia-induced increase in Vc was largely independent of a change in $\dot{Q}$. This is in agreement with previous findings in the dog lung where substantial recruitment of the pulmonary capillaries occurred in response to hypoxia despite, in some cases, a fall in $\dot{Q}$ (Wagner et al. 1975). Accordingly, we propose that, as in the dog lung, alterations in $\dot{Q}$ contribute only minimally to pulmonary capillary recruitment in response to short-term hypoxia in healthy humans.

4.3.2. Hypoxia-induced alterations in left ventricular relaxation—The second mechanism by which hypoxia may have elicited recruitment of the pulmonary capillaries relates to a potential increase in LA pressure. It has been shown previously that LV diastolic function is compromised in response to hypoxia (Kjaergaard et al. 2006; Pham et al. 2010)

and high altitude (Allemann et al. 2004). It can be postulated that such impairment in LV relaxation would increase LV pressure with a concomitant increase in LA pressure. In theory, an increase in LA pressure would likely contribute to hypoxia-induced pulmonary capillary recruitment through a retrograde rise in pulmonary capillary pressure. However, LA pressure has been shown to either remain constant or be elevated only slightly with short-term hypoxia in both animals (Wagner et al. 1975) and humans (Maggiorini et al. 2001). Moreover, pulmonary capillary recruitment did not correlate with alterations in LA pressure in anesthetized dogs (Wagner et al. 1975). In the present study, hypoxic exposure impaired LV relaxation, as demonstrated by a reduction in e' and an increase in IVRT. However, in agreement with the aforementioned findings however (Wagner et al. 1975) V_c was not correlated significantly with either e' or IVRT, regardless of whether assessed as absolute values or the percent changes from pre- to post-hypoxia (Fig. 4 and Fig. 5). Multiple linear regression analysis demonstrated that ~6% of the hypoxia-induced increase in V_c was explained by the reduction in e' (Table 3). Therefore, we propose that, like in the dog, impairment of LV relaxation with a consequent increase in LA pressure is likely not a primary mediator of pulmonary capillary recruitment in response to hypoxia in healthy humans.

4.3.3. Hypoxic pulmonary vasoconstriction—Hypoxic pulmonary vasoconstriction (HPV) is a vasomotor property intrinsic to the lungs whereby alveolar hypoxia elicits constriction of the pulmonary vasculature to better distribute blood flow to optimally ventilated lung segments. The precise mechanisms that underpin HPV remain controversial, but likely include endothelium release of the vasoactive peptide endothelin-1, calcium sensitization of the contractile apparatus, and a change in the redox status of an oxygen sensitive potassium channel or channels leading to hypoxic inhibition of voltage gated potassium channels in pulmonary artery smooth muscle cells (reviewed by (Moudgil et al. 2005). Although HPV is thought to occur primarily in pre-capillary pulmonary artery and arterioles (Hoshino et al. 1988; Leach et al. 1994; Barnes et al. 1995), several studies have shown that hypoxia also elicits vigorous constriction of the post-capillary pulmonary vessels in a variety of species (Sheehan et al. 1992; Zhao et al. 1993; Zhao et al. 1995; Hillier et al. 1997). Moreover, in some instances, hypoxic exposure has been shown to induce a significantly greater magnitude of constriction in the pulmonary vein compared to the pulmonary artery (Zhao et al. 1993). For example, in the dog lung, Hillier et al. (Hillier et al. 1997) reported a significant reduction in subpleural venular as well as subpleural arteriolar diameter in response to acute hypoxia. Moreover, the authors reported that this constriction was reversed when the vasodilator nitric oxide was added to the hypoxic mixture, suggesting that both the pre- and post-pulmonary capillary vessels undergo active constriction in response to hypoxia. In addition, Zhao et al. (Zhao et al. 1993) demonstrated that the constrictor response to severe hypoxia was significantly greater in pulmonary venous smooth muscle relative to pulmonary arterial smooth muscle in the rat. While we are unaware of any such direct evidence that the pulmonary post-capillary vasculature undergoes hypoxia-induced constriction in humans, Maggiorini et al. (Maggiorini et al. 2001) demonstrated that 10 minutes of alveolar hypoxia elicited a significant increase in pulmonary capillary pressure (Ppc) despite no change in pulmonary wedge pressure and normal left atrial pressure in 14 healthy humans. It is possible that the hypoxia-induced increase in Ppc occurred secondary to an increase pressure downstream of the pulmonary capillaries due to constriction of the post-capillary vessels. Furthermore, chronic hypoxia has been shown to induce remodeling of the human pulmonary vein, including intimal and adventitial thickening, arterialization, and an increase in the number of smooth muscle cells, similar to that observed in the pulmonary artery (Wagenvoort et al. 1976; Chazova et al. 1995). These data provide evidence that both pre- and post-pulmonary capillary vessels are somewhat involved in the pulmonary constrictor response to hypoxia in humans.

In the present study, we observed a significant increase in V_c (42%) in response to hypoxic exposure, suggesting that hypoxia facilitates pulmonary capillary recruitment in healthy humans. Theoretically, hypoxia-mediated constriction of the pre- and/or post-pulmonary capillary vessels may have contributed somewhat to this increase in pulmonary capillary recruitment. While a general constriction of the pre-capillary pulmonary vessels may have increased P_{pa} sufficiently to overcome the normally existing perfusion gradient imposed by gravity increasing pulmonary capillary recruitment secondary to a redistribution of blood flow to the upper segments of the lung, a hypoxia-induced constriction of post-capillary pulmonary vessels may have facilitated recruitment of the pulmonary capillaries through a retrograde rise in pulmonary capillary pressure (Wagner et al. 1979). Presently, we observed an increase in sP_{pa} in every subject from pre- to post-hypoxia. However, while there was a weak but significant relationship between absolute values of V_c and sP_{pa} (Fig. 4), the pre- to post-hypoxia percent change in V_c was not related to the change in sP_{pa} (Fig. 5). Moreover, multiple regression analysis suggested that only ~2% of the pre- to post-hypoxia variance in V_c was explained by the increase in sP_{pa} (Table 3). Based on these data, it can be postulated that an increase in sP_{pa} secondary to constriction of the pre-capillary pulmonary vessels is not a primary mediator of hypoxia induced pulmonary capillary recruitment in healthy humans. Overall, only ~37% of the hypoxia-mediated increase in V_c (i.e. pulmonary capillary recruitment) was accounted for by alterations in $\dot{Q}$, sP_{pa} and LV diastolic function. That is, it is likely that mechanisms other than increases in cardiac output, pressure within the pre-capillary pulmonary vessels and left atrial pressure contribute to the pulmonary capillary recruitment associated with hypoxia in healthy humans. Accordingly, we speculate that constriction of the post-capillary pulmonary vessels may be a potential mediator of hypoxia-induced pulmonary capillary recruitment in healthy humans.

4.4. Why Do Our Human Findings Not Agree With Findings in The Dog?

Exactly why constriction of the post-capillary pulmonary vessels in response to hypoxia would, at least in part, mediate pulmonary capillary recruitment in human but not the dog lung is uncertain. One potential cause is the considerable variation in distensibility of the pulmonary vasculature between species. For example, in dog (Maloney et al. 1970) and rabbit (Caro et al. 1965) lungs, the pulmonary vein is less distensible than the pulmonary artery, primarily because of a larger fibrous tissue and collagen content of the vessel wall, which in turn makes the veins in these species less vasoactive. By contrast, in species such as the sheep, the pulmonary vein is highly muscularized and demonstrates significant vasoreactivity (Kay 1983). Therefore, it can be postulated that the disparity between the findings of the present study and of those of Wagner et al. (Wagner et al. 1979) is attributable to species related differences in pulmonary arterial and venous vessel structure and vasoreactivity.

4.5. Conclusion

In conclusion, hypoxic exposure elicits pulmonary capillary recruitment in healthy humans, as evidenced by an increase in pulmonary capillary blood volume. However, the recruitment of the pulmonary capillaries was mediated only in part by changes in cardiac output, pulmonary artery systolic pressure, and altered left ventricular relaxation. We speculate that these data may circuitously identify hypoxic pulmonary venoconstriction as a potential contributor to hypoxic pulmonary capillary recruitment in healthy humans.

Acknowledgments

Grants

This work was supported by National Heart, Lung, and Blood Institute Grant HL-71478. BJT is supported by a Fulbright Commission UK Distinguished Scholar Award.

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Fig. 1.

Testing protocols for saline infusion and hypoxic exposure trials. At visit 1, subjects underwent rapid intravenous saline infusion (30 ml·kg⁻¹ over ~15 min). At visit 2, subjects were exposed to 17-h of normobaric hypoxia (FiO₂ 12.5%, barometric pressure 732 mmHg) in a hypoxic tent. Pulmonary function (striped up arrow) was assessed at visit 1 before saline infusion. Cardiac output and pulmonary capillary blood volume were assessed via a rebreathe technique before and after saline infusion and hypoxic exposure (closed up arrows). Echocardiographic estimates of cardiac output, pulmonary artery systolic pressure and left ventricular diastolic function were also made before and after hypoxic exposure prior to the rebreathe maneuvers (open up arrow). *Two visits separated by at least 48 hours.

Fig. 2. Individual subject (dashed lines) and group mean (solid lines) cardiac output ($\dot{Q}$), pulmonary capillary blood volume (V_c), and V_c relative to $\dot{Q}$ before (pre) and after (post) rapid saline infusion (A, C and E, respectively) and 17-h hypoxic exposure (B, D and F, respectively). Group mean values for 25 subjects. * $P < 0.05$, ** $P < 0.01$; group mean values significantly different before vs. after hypoxic exposure.

Fig. 3. Individual subject (dashed lines) and group mean (solid line) echocardiographically determined pulmonary artery systolic pressure (sPpa) (A), peak early septal mitral annular relaxation velocity (e') (B) and left ventricular isovolumetric relaxation time (IVRT) (C) before (pre) and after (post) 17-h hypoxic exposure. Group mean values for 25 subjects (sPpa) and 14 subjects (e' and IVRT). ** $P < 0.01$; group mean values significantly different before vs. after hypoxic exposure.

Fig. 4.

Scatter-plots showing relationships between the individual subject absolute values of pulmonary capillary blood volume (V_c) and cardiac output ($\dot{Q}$) (A), pulmonary artery systolic pressure (sPpa) (B), peak early septal mitral annular relaxation velocity (e') (C) and left ventricular isovolumetric relaxation time (IVRT) (D). Data points represent 25 subjects for $\dot{Q}$ and sPpa, and 14 subjects for e' and IVRT. Data from both pre- and post-hypoxia measures are shown such that there are two data points per subject. * $P < 0.05$; significant correlation between two variables.

Fig. 5.

Scatter-plots showing relationships between the individual subject percent change in pulmonary capillary blood volume (V_c) and the percent change in cardiac output ($\dot{Q}$) (A), pulmonary artery systolic pressure (sPpa) (B), peak early septal mitral annular relaxation velocity (e') (C) and left ventricular isovolumetric relaxation time (IVRT) (D) from pre- to post-hypoxic exposure. Data points represent 25 subjects for $\dot{Q}$ and sPpa, and 14 subjects for e' and IVRT.

Table 1
Baseline pulmonary function

	Absolute	% predicted
FVC, L	5.12 ± 0.18	103 ± 3
FEV ₁ , L·s ⁻¹	4.12 ± 0.15	99 ± 3
FEV ₁ :FVC, %	81 ± 1	98 ± 1
FEF ₂₅₋₇₅ , L·s ⁻¹	4.68 ± 0.51	96 ± 4

FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; FEF₂₅₋₇₅, forced expiratory flow between 25% and 75% of FVC. % predicted values calculated from Quanjer et al. (Quanjer et al. 1993). Values are group means ± SEM for 25 subjects.

Table 2
Physiological responses and echocardiographically derived measures of cardiac function
before and after hypoxic exposure

	Pre-hypoxia	Post-hypoxia
SpO ₂ , %	98 ± 1	83 ± 3 ^{**}
SBP, mmHg	114 ± 2	117 ± 2
DBP, mmHg	77 ± 3	71 ± 1
MAP, mmHg	90 ± 2	86 ± 4
f _H , beats·min ⁻¹	60 ± 7	75 ± 11 ^{**}
SV, ml	77 ± 15	71 ± 12 [*]
Q̇, L·min ⁻¹	4.8 ± 1.0	5.1 ± 0.9
E, cm·s ⁻¹	74 ± 14	71 ± 12
A, cm·s ⁻¹	49 ± 9	59 ± 15 [*]
E/A	1.6 ± 0.4	1.3 ± 0.2 [*]
e', cm·s ⁻¹	11.0 ± 3.1	8.7 ± 2.4 ^{**}
a', cm·s ⁻¹	7.6 ± 1.2	7.3 ± 1.1
e'/a'	1.5 ± 0.9	1.2 ± 1.3 [*]

SpO₂, arterial oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; f_H, heart rate; SV, stroke volume; Q̇, cardiac output; E, early transmitral flow velocity; A, late transmitral flow velocity; e', peak early septal mitral annular relaxation velocity; a', peak late septal mitral annular relaxation velocity. Values are group means ± SEM for 25 subjects (SpO₂, SBP, DBP and MAP) and for 14 subjects (all other variables).

* $P < 0.05$

** $P < 0.01$; values significantly different to pre-hypoxic exposure.

Table 3
Multiple regression parameters showing the influence of cardiac output, pulmonary artery systolic pressure and peak early septal mitral annular velocity on pulmonary capillary blood volume

Parameter	β coefficient	Semi-partial r^2	p -value
<i>Absolute values</i>			
$\dot{Q}$, L·min ⁻¹	11.55	0.086	0.139
sPpa, mmHg	0.71	0.013	0.378
e' , cm·s ⁻¹	6.43	0.145	0.046
<i>% change</i>			
% $\Delta \dot{Q}$, L·min ⁻¹	1.93	0.291	0.068
% Δ sPpa, mmHg	-0.17	-0.018	0.557
% $\Delta e'$, cm·s ⁻¹	0.27	0.055	0.876

% Δ , percent change in values from pre- to post-hypoxic exposure. $\dot{Q}$, cardiac output; sPpa, pulmonary artery systolic pressure; e' , peak early septal mitral annular relaxation velocity. The data used in the multiple regression analysis was taken from the 14 subjects who underwent the rebreath assessment of $\dot{Q}$ and pulmonary capillary blood volume as well as the echocardiographic assessment of sPpa and e' . Data from both pre- and post-hypoxia measures of $\dot{Q}$, sPpa and e' were included in the analysis of absolute values.