Adverse Effects of Normovolemic Polycythemia and Hypoxia on Hemodynamics in the Dog

ROBERT L. MCGRATH AND JOHN V. WEIL

SUMMARY Although polycythemia commonly occurs in hypoxic patients, most hemodynamic studies of polycythemia have been done in the normoxic state. We studied the combined effects of polycythemia and hypoxia. In 11 splenectomized, anesthetized dogs, hematocrit was increased from $42.6 \pm 1.2$ to $65.5 \pm 0.6\%$ (SEM) by isovolumic exchange transfusions with fresh canine packed RBC's. Studies were conducted during normoxia ($P_{\text{ao2}} = 113.8 \pm 4.2 \text{ mm Hg}$) and hypoxia ($P_{\text{ao2}} = 40.5 \pm 1.6 \text{ mm Hg}$). Polycythemia alone increased pulmonary vascular resistance by $112 \pm 4.6\%$ ($P < 0.01$) and hypoxia alone increased pulmonary vascular resistance by $141 \pm 11.4\%$ ($P < 0.01$). Combined hypoxia and polycythemia increased pulmonary vascular resistance by $308 \pm 28.1\%$ ($P < 0.005$), an effect significantly greater than that of hypoxia or polycythemia alone ($P < 0.005$). In contrast, systemic vascular resistance increased with polycythemia by $90 \pm 8.8\%$ ($P < 0.01$), whereas hypoxia had no effect on systemic vascular resistance either alone or when combined with polycythemia. Polycythemia decreased cardiac output by $50 \pm 1.8\%$ ($P < 0.01$), whereas hypoxia had no significant effect alone or when combined with polycythemia. Oxygen transport was decreased by polycythemia by $29 \pm 0.8\%$ ($P < 0.01$) due to decreased cardiac output. Hypoxia decreased oxygen transport by $28 \pm 0.9\%$ ($P < 0.01$) due to a decrease in arterial oxygen content. Combined hypoxia and polycythemia decreased oxygen transport by $50 \pm 2.6\%$ ($P < 0.01$) an effect greater than that of hypoxia or polycythemia alone. In four control dogs, exchange with whole blood produced no change in the variables studied. Synergistic effects of hypoxia and polycythemia on pulmonary vascular resistance reflect combined influences of increased blood viscosity and hypoxic pulmonary vasoconstriction. Such a combination may contribute to the occurrence of cor pulmonale in patients with hypoxia and secondary polycythemia.

POLYCYTHEMIA is common in patients with hemoglobin desaturation secondary to hypoxia.\(^1\text{4}\) This development, mediated by increased erythropoietin production\(^2\) in response to hypoxemia, would seem to be beneficial, resulting in increased oxygen transport. However, the advantage of an increased oxygen-carrying capacity of blood appears to be offset by hyperviscosity-induced increases in vascular resistance with a resulting decrease in cardiac output.\(^6\text{14}\) In fact, there is little support for the notion that hematocrits substantially above normal are useful.\(^15\)

Previous studies\(^6\text{13}\) have examined the effects of polycythemia on hemodynamics in the normoxic state. However, the hypoxia which accompanies secondary polycythemia might modify the effects of the latter. Specifically, hypoxia could cause systemic vasoconstriction offsetting the increased resistance of hyperviscosity, or could produce pulmonary vasoconstriction with increased pulmonary vascular resistance\(^16\) and augment the effects of altered viscosity. Thus hypoxia might reduce or magnify the oxygen transport deficit induced by polycythemia.

The hemodynamic responses to acute hypoxia, acute polycythemia and the combination of polycythemia and hypoxia, were examined in dogs. We found that hypoxia did not reverse the decrease in cardiac output resulting from polycythemia, and the adverse effect of polycythemia on systemic oxygen transport and pulmonary vascular resistance were magnified.

Methods

Eleven mongrel dogs weighing 12.7–19.1 kg (mean 15.6 kg) were studied, using a single dose of pentobarbital anesthesia (25 mg/kg, iv). Ventilation was controlled by a Harvard respirator. The dogs had been splenectomized 2 weeks previously to eliminate splenic contraction which could cause the hematocrit to vary. Through the femoral vessels, polyethylene catheters were placed in the right atrium, main pulmonary artery, and ascending aorta. The dogs were given 5000 U of intravenous heparin. Arterial and mixed venous pH and blood gas tensions were measured with standard electrodes (Radiometer). Blood oxygen saturation was measured with an oximeter (American Optical). Blood oxygen content was calculated from the sat-
ulation and hemoglobin concentration, the latter measured colorimetrically (cyanmethemoglobin). Hematocrits were measured by the microhematocrit technique. Blood pressures were recorded from Statham P23-D strain gauges on an Electronics for Medicine recorder. Cardiac output was determined using the indicator dilution method (indocyanine green) with a calibrated cuvette densitometer (Waters Corporation model XC100A). Systemic vascular resistance was calculated by dividing the difference of mean arterial pressure and mean right atrial pressure by cardiac output. Pulmonary vascular resistance (PVR) was calculated as the ratio of mean pulmonary artery pressure to cardiac output. These resistances are expressed in hybrid resistance units (mm Hg/min per liter).

Packed red blood cells used to induce polycythemia were prepared by centrifuging fresh heparinized canine blood for 30 minutes at 3000 rpm. The cells were kept in a constant temperature bath at 37°C until needed and were infused within 1 hour after removal from the donor animal.

The experimental procedure was as follows: Each dog was used as its own control. Blood gases, pressures, and cardiac output were measured during normoxia, and while the dog breathed a mixture of 30% oxygen in nitrogen (Pao2 = 113.8 ± 4.2 mm Hg). These measurements again were determined during hypoxia produced by inhalation of 12% oxygen in nitrogen for 15 minutes (Pao2 = 40.5 ± 1.6 mm Hg). The dog then was allowed to recover and stabilize while being ventilated with 30% oxygen. An exchange transfusion then was given in which whole blood was removed and packed cells were infused in equal volume. The total exchanged volume was calculated to increase the hematocrit to levels greater than 60%. At increments of approximately 10%, hemodynamic data were determined during normoxia 15-20 minutes following the exchange, when variables had stabilized. Measurements then were repeated after 15 minutes of hypoxia. Blood volume was determined at the beginning and at the end of each experiment using autologous 51Cr-labeled red cells. In four dogs that served as controls, similar exchange transfusions with whole blood were carried out over a comparable time. No significant differences were noted in the measured hemodynamic variables of the control dogs when compared with the baseline values of the study dogs.

Data were analyzed by two-way analysis of variance and paired comparisons were made by Newman-Keuls multiple range tests.

Results

Table 1 summarizes hemodynamic data from 11 dogs during normoxia and hypoxia at only the low and high hematocrits. The isovolumic exchange transfusions with packed RBC's increased the hematocrit from 42.6 ± 1.2% (SEM) to 65.5 ± 0.6% (P < 0.01) while blood volume remained unchanged. Prior to exchange transfusion, ventilation with 30% oxygen produced a normoxic Pao2 of 113.8 ± 4.2 mm Hg; with polycythemia this increased slightly to 125.9 ± 4.9 (P < 0.05). With 12% oxygen at the low control hematocrit, Pao2 was 40.5 ± 1.6 mm Hg and again increased with polycythemia (Pao2 = 44.0 ± 2.1 mm Hg) (P < 0.05). These increases were not due to changes in ventilation because the Paco2 was unchanged and ventilation was controlled by respirator.

The decrease in arterial pH during normoxic polycythemia probably reflects metabolic acidosis from local tissue hypoperfusion. Compared with normoxic normocythemia, the arterial PCO2's are the same, and thus no respiratory component to the acidosis is suggested. Also, fresh heparinized blood was used for the exchange, and thus the acidemia probably is not induced by this procedure.

Effects on cardiac output and its components are shown in Figure 1. Hypoxia produced no changes in cardiac output at the low and high hematocrits. In contrast, polycythemia decreased it by 50% from 2.21 ± 0.2 to 1.08 ± 0.1 liters/min. Hypoxia alone augmented the heart rate by 27%, whereas polycythemia alone had no significant effect. Also, the combination of hypoxia and polycythemia did not change heart rate from the initial value. Stroke volume was decreased by 8% by hypoxia (Fig. 1) and by 45% by polycythemia. The combination of hypoxia and polycythemia produced a decrease not significantly different from that of polycythemia alone.

Hypoxia reduced oxygen transport by 28% from 43.2 ± 3.1 to 31.2 ± 2.6 ml/min (P < 0.01) (Fig. 2). This reflected decreased arterial oxygen content (Fig. 2) which was reduced by 30% while cardiac output was unchanged by hypoxia. Similarly, polycythemia decreased oxygen transport by 29%, due to a decrease in cardiac output. This decrease in cardiac output was greater than the relative increase in arterial oxygen content. Combined hypoxia and polycythemia decreased oxygen transport, more than either alone, by 50% from 43.2 ± 3.1 to 21.5 ± 1.4 ml/min (P < 0.01). This reflected combined depressant effects on arterial oxygen content and cardiac output.

The pulmonary and systemic vascular resistances during hypoxia and polycythemia are shown in Figure 3. Hypoxia increased pulmonary vascular resistance (PVR) by 141% and polycythemia augmented PVR by 112% (Fig. 3A). With combined hypoxia and polycythemia, PVR increased by 308% from 5.2 ± 0.4 to 21.2 ± 2.0 U (P < 0.01). This combined effect was significantly greater than that of hypoxia or polycythemia alone. Mean pulmonary arterial pressure increased with hypoxia by 130%. Polycythemia had no significant effect on pulmonary artery pressure but, when combined with hypoxia, increased it by 127%. This combined effect
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| TABLE 1 Hemodynamic Data in 11 Dogs Made Polycythemic by Isovolumic Exchange Transfusion during Normoxia and Hypoxia |

<table>
<thead>
<tr>
<th>Normocytzemias</th>
<th>Polycytzemias</th>
<th>Percent change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoxia (N)</td>
<td>Hypoxia (H)</td>
<td>N → H</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>42.6 ± 12.1</td>
<td>42.4 ± 2.1</td>
</tr>
<tr>
<td>Heart rate</td>
<td>153.6 ± 11.3</td>
<td>188.2 ± 7.7</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>2.21 ± 0.02</td>
<td>2.30 ± 0.01</td>
</tr>
<tr>
<td>(P_{A0})</td>
<td>129.3 ± 16.2</td>
<td>143.2 ± 11.3</td>
</tr>
<tr>
<td>(P_{VR})</td>
<td>10.2 ± 3.1</td>
<td>22.5 ± 3.1</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>63.8 ± 12.4</td>
<td>71.6 ± 12.4</td>
</tr>
<tr>
<td>(SO_2T)</td>
<td>43.2 ± 3.2</td>
<td>43.6 ± 1.1</td>
</tr>
<tr>
<td>(Cao_2)</td>
<td>19.6 ± 3.1</td>
<td>13.72 ± 2.2</td>
</tr>
<tr>
<td>Blood volume</td>
<td>1.37 ± 0.04</td>
<td>1.39 ± 0.06</td>
</tr>
</tbody>
</table>

Results in columns 2 through 8 are expressed as mean ± SE.

P < 0.05; \(* = P < 0.01.

was similar to that of hypoxia alone. In contrast to PVR, systemic vascular resistance (SVR) (Fig. 3B) was not significantly changed by hypoxia 63.8 ± 5.6 vs. 71.6 ± 12.1 \(U\) (\(P\) not significant), but was augmented by 90% by polycythemia. The combination of hypoxia and polycythemia increased SVR by 101%. This combined influence was not greater than that of polycythemia alone. The mean systemic blood pressure increased with hypoxia at both low and high hematocrits. Polycythemia alone or in combination with hypoxia had nonsignificant effects on the mean systemic pressure.

**CARDIAC OUTPUT = HEART RATE x STROKE VOLUME**

**SYSTEMIC OXYGEN TRANSPORT = ARTERIAL OXYGEN CONTENT x CARDIAC OUTPUT**

**FIGURE 1 Cardiac output and its components, stroke volume and heart rate, during hypoxia and polycythemia. Cardiac output was decreased by polycythemia independent of oxygenation. Heart rate increased during hypoxia, an effect which was attenuated by polycythemia. Stroke volume was decreased by polycythemia. Vertical lines through circles indicate standard error of the mean; asterisks indicate \(P < 0.01\).**

**FIGURE 2 Systemic oxygen transport (SO_2T) was decreased by both hypoxia and polycythemia but to a greater extent by the combination. This reflected a depression of arterial oxygen content (Cao_2) by hypoxia and a decrease in cardiac output due to polycythemia. Asterisks indicate \(P < 0.01\).**
Figure 3  A: Pulmonary vascular resistance (PVR) was increased by both polycythemia and hypoxia and to a greater extent by the combination. The mean pulmonary arterial pressure (Ppa) was increased by hypoxia but unaffected by polycythemia. Asterisks indicate $P < 0.01$. B: Systemic vascular resistance (SVR) was increased by polycythemia and unaffected by hypoxia. The mean arterial pressure (Pao) was increased by hypoxia at the low hematocrit but was not significantly altered by polycythemia or hypoxic polycythemia.

Figure 4 shows a single dog's hemodynamic response to normoxia and hypoxia at four increasing hematocrit levels. All dogs showed similar responses.

Discussion

Polycythemia and hypoxia both decreased systemic oxygen transport. This reflected decreased cardiac output during polycythemia and decreased blood oxygen content during hypoxia. When polycythemia and hypoxia were combined, the decrements in oxygen transport were greater than with either alone. Similarly, PVR was augmented by both polycythemia and hypoxia. When these were combined, a larger increase was found which was greater than additive; that is, polycythemia and hypoxia acted synergistically to increased PVR. In contrast, systemic vascular resistance was increased by polycythemia, but not by hypoxia; the combined effects were similar to that of polycythemia alone.

Murray et al.,6,7 Weiss and his colleagues,9 and Richardson and Guyton8 studied the hemodynamic responses to acute polycythemia and found decreases in cardiac output and oxygen transport. There was little change in pulmonary and systemic blood pressures, but pulmonary and systemic vascular resistances increased. The fall in cardiac output with polycythemia was proportionately greater than the rise in oxygen content accounting for the decrement in oxygen transport. These results are similar to ours during normoxia. The decrease in cardiac output is traditionally attributed to the effects of viscosity on systemic vascular resistance. We found that hypoxia produced no significant change in the decreased cardiac output due to polycythemia. However, hypoxia did increase heart rate, but to a lesser degree during polycythemia than during normocytopenia. That polycythemia depresses stroke volume has been demonstrated previously, and this effect has been attributed to increased blood viscosity and decreased venous return.6,10,14 Although we can find no studies of ventricular function in polycythemia, it may be decreased since Altland and Highman15 found myocardial lesions in rats made polycythemic and exposed to hypoxia. The lesions were attributed to decreased myocardial perfusion. Recently, Hoffman et al.19 found that in dogs made acutely polycythemic and hypoxic subendocardial blood flow was reduced. This reduced flow then may produce myocardial dysfunction. The question of whether increased vascular resistance is the cause of depressed cardiac output is not resolved by this study. Pulmonary vascular resistance showed the largest increases but it is an unlikely explanation because cardiac output and pulmonary vascular resistance were not correlated; the largest increase in pulmonary vascular resistance occurred when polycythemia and hypoxia were combined whereas the greatest decrement in cardiac output was seen with polycythemia alone. Changes in systemic resistance were less dramatic but more closely correlated with...
alterations in cardiac output suggesting that SVR may limit blood flow. However, with a failing heart increased pulmonary vascular resistance might impose significant flow limitations.

Synergistic effects of polycythemia and hypoxia on the pulmonary vascular resistance are not surprising. Murray et al. and Tyson have shown that an increase in hematocrit increased pulmonary vascular resistance, presumably due to increased blood viscosity. Airway hypoxia is well known to cause pulmonary arterial vasoconstriction and hypoxemia decreases the deformability of red blood cells; both of these changes may increase the resistance to blood flow through pulmonary capillaries. Figures 3A and 4 show that with increasing polycythemia there is a steeper rise in PVR with hypoxia. Because the degree of hypoxia was unchanged when PVR was measured at the increasing hematocrits, this steeper curve probably reflects the increasing viscosity with polycythemia plus the effects of hypoxia on red cell deformity. Recently Hoffman et al., studying hypoxic polycythemia, found much milder increases in the pulmonary vascular resistance than we did. This may reflect increased reactivity of pulmonary vascular bed in our dogs acclimatized to moderate altitude (Denver 1600 m) compared to their dogs at sea level. Because hypoxic pulmonary vasoconstriction is more dependent on airway hypoxia than on arterial hypoxemia, this synergism between hypoxia and polycythemia might be greater in disorders of alveolar hypoventilation than in situations in which hypoxemia arises from right-to-left intracardiac shunts. In this study, pulmonary vascular resistance was measured as an index of right ventricular afterload. Because left atrial pressure was not measured, we cannot separate the potential contributions of increased left atrial pressure from those of increased pulmonary arteriolar resistance. In current unpublished studies we find no significant increases in left atrial pressure during hypoxic polycythemia, suggesting that increased pulmonary vascular resistance largely reflects increased pulmonary arteriolar resistance.

The increased systemic vascular resistance with normoxic polycythemia found in this study agrees with previous reports. However, in contrast to the finding for the pulmonary bed, superimposing hypoxia on polycythemia had no effect on the systemic vascular resistance additional to that of polycythemia alone because hypoxia did not constrict systemic vessels. Hypoxia did not produce systemic vasodilation as often is reported. The explanation may be that ventilation was controlled by a respirator in our studies. Kontos et al. have shown that when ventilation is controlled the systemic vasodilator response to hypoxia is abolished. Perhaps the systemic vasodilation to be expected in spontaneously breathing animals would minimize the impediment to blood flow due to polycythemia and reduce the adverse effects on oxygen transport. Pentobarbital anesthesia probably did not have a significant effect on the pulmonary and systemic vascular responses to polycythemia because Weisse et al. found similar increases in the pulmonary and systemic vascular resistances with acute polycythemia in both awake and anesthetized dogs.

We studied acute polycythemia in anesthetized dogs. The slight fall in arterial pH associated with acute polycythemia would shift the Hb-O2 dissociation curve rightward and allow increased extraction of oxygen in systemic capillaries. However, during alveolar hypoxia, oxygen loading in the lung would occur on the steep portion of the dissociation curve and would be decreased by acidosis—an effect which might largely cancel the increased unloading in tissues. The relevance of our findings to the chronic situation is unclear. Smith and Crowell in studies on the effects in dogs of chronic polycythemia induced by high altitude hypoxia, showed that the optimal hematocrit for survival was shifted to a higher value. This may have been due to an increased vascularity which reduced the diffusion distance between capillaries and cells. This may be beneficial in maintaining adequate tissue oxygenation in the chronic situation, a result which our study does not support, but the cost of this in terms of vascular resistance and effects on the heart was not studied. Rosenthal and Fyler studied polycythemic children with cyanotic congenital heart lesions and found for certain defects that lowering the hematocrit led to an increase in pulmonary blood flow and a reduction in pulmonary vascular resistance. Thus, chronic polycythemia is associated with sustained increases in pulmonary vascular resistance and decreases in cardiac output. Abraham et al. studied patients with chronic bronchitis with alveolar hypoventilation and polycythemia. Responses to oxygen and acetylcholine led to the suggestion that pulmonary hypertension in these patients was due primarily to pulmonary vasoconstriction resulting from hypoxia.

In summary, combined hypoxia and polycythemia pose an especially severe threat to circulatory oxygen transport. Their combined effects on PVR may predispose to cor pulmonale in the hypoxic polycythemic patient.

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References


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