Acute alveolar hypoxia increases blood-to-tissue albumin transport: role of atrial natriuretic peptide

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Increased irANP from 211 rats to graded alveolar hypoxia. We showed that concentration (irANP) produced by exposure of anesthetized rats to hypoxic ventilation (n = 5–7/group). Hypoxia (10 min) increased irANP from 211 ± 29 (room air) to 229 ± 28 (15% O2, not significant), 911 ± 205 (10% O2), and 4,374 ± 961 pg/ml (8% O2), respectively. Graded increases in C RSA were significant at 8% O2 in fat (3.6-fold), ileum (2.2-fold), abdominal muscles (2.0-fold), kidney (1.8-fold), and jejunum (1.4-fold). C RSA was decreased in back skin and testes; heart, brain, and lungs were unaffected. The increases in C RSA were related to irANP and not to arterial PO2. Circulating plasma volume was negatively correlated with whole body C RSA. Graded increases in extravascular water content (EVW) were found in the kidney, left heart, and cerebrum and were positively related to C RSA in the kidney. EVW decreased in gastrointestinal tissues; the magnitude was inversely related to C RSA. We conclude that ANP-induced protein extravasation contributes to plasma volume contraction during acute hypoxia.

IN A COMPANION PAPER (1), we described the changes in plasma immunoreactive atrial natriuretic peptide concentration (irANP) produced by exposure of anesthetized rats to graded alveolar hypoxia. We showed that within 10 min of ventilation with 10% or 8% O2, there was a large increase in plasma irANP that was sustained throughout a 50-min period of hypoxia. There was also an early decrement in plasma volume (PV) and a corresponding increase in hematocrit, with little change in plasma protein concentration. Similar reductions in intravascular volume are produced by intravenous administration of ANP, suggesting that this peptide acts at the capillary membrane to increase permeability to fluid and plasma proteins (2, 19). Subsequent studies utilizing direct measurements of plasma protein transport in intact rats (18, 24) and in single capillaries of frog mesentery (6) have corroborated this view.

The purpose of the present study was to evaluate the role of ANP in mediating increases in protein and fluid extravasation during acute hypoxia. These are the same experiments as reported in the companion paper (1); however, here we focus on events occurring at the tissue level. Blood-to-tissue albumin transport was measured in multiple tissues by using a sensitive double-isotope technique. PV and extravascular water (EVW) contents of individual tissues were also assessed. Our main finding was that ventilation hypoxia increased albumin extravasation into abdominal muscles, visceral fat, kidney, and gastrointestinal tissues in a dose-dependent manner. Of all the parameters measured, irANP was the best predictor of albumin extravasation in these tissues. The importance of hypoxia-induced protein extravasation to fluid shifts occurring at whole-animal and tissue levels is discussed.

METHODS

General. Measurements of blood-tissue transport were made over the last 35 min of the 50-min gas treatment period in the four groups of rats described in the companion paper (1). Details of the experimental setup and hypoxia protocols are provided in the companion paper, with this paper reporting only those procedures related to the albumin transport. Briefly, male Wistar rats (Charles River, Kingston, NY) weighing 260–320 g were anesthetized with pentobarbital sodium (12 mg/100 g) administered subcutaneously in two depots over a 1-h period. Arterial and venous cannulas were inserted for pressure measurement, infusion of fluids and tracers, and for collection of blood samples. A tracheal cannula was inserted through a neck incision, and the opposite end was attached to a rodent ventilator for mechanical ventilation during gas treatment. Pentobarbital sodium was given intravenously as needed to maintain anesthesia.

Experimental protocols. Four groups of animals (n = 5–7) were studied: normoxic controls (room air) and three hypoxic (15, 10, and 8% O2-balance N2) groups. Gas treatment was applied via a Douglas bag attached to the ventilator. Baseline blood samples were taken 10 min before the start of the gas treatment period (time t = −10 min). A second set of blood samples was collected after 10 min of gas treatment (t = 10 min). Albumin extravasation was measured during the last 35 min of the gas ventilation by using a double-isotope subtraction technique (15). To start the measurement, 131I-labeled rat serum albumin (131I-RSA, 6 µCi) was injected intravenously at t = 15 min. Blood samples (100 µl) were collected 20 and 30 min after the start of gas treatment and 5 and 15 min after isotope infusion for measurement of plasma 131I activity. These blood samples were replaced with similar volumes of lactated Ringer solution. At t = 45 min (30 min after 131I-RSA injection), the clearance measurement was completed by injection of 125I-RSA (6 µCi), which served as a “reference tracer” for measurement of tissue intravascular blood volumes. Terminal blood samples were collected 5 min later at t = 50 min after the start of gas ventilation (35 min after injection of 131I-RSA). The rats were then killed with intravenous KCl, and selected tissues were collected for determination of radioactivity and water content. As described in the companion paper (1), the amounts of injected 131I-RSA and 125I-RSA were known, enabling the 20- and 50-min samples to be used to calculate circulating PV at these times.

Blood samples were centrifuged, and aliquots of plasma were diluted to 1 ml and placed in count tubes for determination of 131I and 125I activities. Uniform tissue samples were rapidly dissected postmortem, blotted, and placed in covered
and purified by anion exchange and repeated concentration-dilution with Minicon filters (Amicon, Danvers, MA). Labeled RSA (specific activity = 10–50 μCi/mg) was repurified on the day of use to reduce free 125I levels to <1%.

Statistics. Data are expressed as means ± SE unless otherwise indicated. Differences among treatment means were tested by using one-way analysis of variance followed by orthogonal contrasts and Duncan's new multiple-range test for post hoc comparisons among individual means. Relationships among variables were evaluated by using linear (simple and multiple) regression analyses. Differences are reported as statistically significant when P ≤ 0.05.

RESULTS

General. Cardiovascular and blood gas data collected under baseline conditions and at different time points during gas treatment are detailed in the companion study (1) and are briefly summarized here. A subset of data collected at the beginning and end of the C_RSA measurement period is recorded in Table 1. Because C_RSA represents albumin extravasation averaged over the last 30 min of the treatment period, pooled averages of irANP, PV, and plasma total protein concentration were also calculated and are summarized in Table 1. Blood gas analyses were not performed on radioactive samples; hence pooled values of arterial Po2 (PaO2) are not included in Table 1 (see Ref. 1 for supplemental blood gas data).

Ventilation with either 15 or 10% O2 for 10 min resulted in a graded reduction in PaO2, from 80 ± 3 to 32 ± 1 Torr, whereas no further reduction in PaO2 was observed during ventilation with 8% O2. Plasma irANP, on the other hand, increased in a dose-dependent fashion in all groups, with an average 20-fold elevation observed in rats ventilated with 8% O2. The irANP response developed gradually in rats ventilated with 15% O2 (PaO2 values between 42 and 50 Torr). A more rapid response was observed with more severe hypoxia (PaO2 values <40 Torr), with large increases in irANP occurring within 10 min and persisting throughout the C_RSA measurement period. The irANP response to hypoxia was also associated with small but significant decreases in circulating PV. Although increases in plasma total protein concentration were also suggested, they were proportionally smaller than the decrements in PV and were not statistically different from control values. Taken together, these data indi-

| Table 1. PaO2, irANP levels, PV, and plasma TP concentrations during normoxic and hypoxic ventilation |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Treatment       | PaO2, Torr      | irANP, pg/ml    | PV, µl/g        | TP, mg/ml       |
|                 | 10 min         | 20 min          | 50 min          | 20 min          | 50 min          |
| Room air        | 7               | 80 ± 3          | 211 ± 29        | 363 ± 0.5       | 53.4 ± 2.2      |
| 15% O2          | 6               | 46 ± 1          | 229 ± 28        | 37.4 ± 1.1      | 51.6 ± 1.0      |
| 10% O2          | 5               | 32 ± 1*         | 911 ± 205*      | 33.2 ± 3        | 52.2 ± 1.6      |
| 8% O2           | 6               | 35 ± 1*         | 4,374 ± 961*    | 32.7 ± 1.4      | 56.1 ± 1.3      |

Values are means ± SE. *No. of rats. PaO2, arterial Po2; irANP, immunoreactive atrial natriuretic peptide; PV, plasma volume; TP, total protein. *Significantly different from room air control, P < 0.05. †Values for each time period were pooled before averaging. ‡PV values are missing in 1 rat due to a technical error, and irANP values from a separate rat were omitted because the 50-min value was an outlier (>3 SD from group mean). §Time from start of gas treatment (clearance of 131I-labeled rat serum albumin was measured between 15 and 50 min).
cate that both fluid and protein were extravasated in the most severely hypoxic groups.

Effect of hypoxia on CRSA. Under normoxic conditions, 131I-RSA extravasation rates into individual tissues were similar to our previous measurements (15, 18). The various tissues and organs represented a 140-fold range of basal CRSA, from 0.029 ± 0.004 µl·min⁻¹·g⁻¹ for fat to 4.05 ± 0.79 µl·min⁻¹·g⁻¹ for lung. The mean effects of graded hypoxic ventilation on CRSA in individual tissues are shown in Fig. 1. One rat from the 15% O₂ group has been omitted from Fig. 1 because its response behavior clearly deviated (>3 SD) from the remainder of the group. This rat exhibited a large increase in plasma irANP at 50 min (2,976 pg/ml), and CRSA was elevated two times or more basal values in several tissues. The remaining five rats ventilated with 15% O₂ exhibited small but significant increases in irANP (+43%) by 50 min with no detectable change in CRSA in any tissue. Four out of five rats ventilated with 10% O₂ showed variable increases in CRSA in one or more tissues; however, group averages were not significantly greater than in controls. In contrast, all six rats ventilated with 8% O₂ exhibited elevated CRSA in multiple tissues, with the average CRSA being significantly higher than room air controls in visceral fat (3.6-fold), ileum (2.2-fold), abdominal muscle (2.0-fold), kidney (1.8-fold), and jejunum (1.4-fold). Higher CRSA values were also noted in the lateral gastrocnemius, cecum, and colon; these differences did not reach statistical significance. In back skin and testis, CRSA was significantly reduced in both 10 and 8% O₂ groups. Brain, heart, and lung clearances did not differ from control values.

Relationship between plasma irANP and CRSA. Figure 2 illustrates changes in CRSA plotted as a function of either PaO₂ (A) or the logarithm of average plasma irANP concentrations (B). All data points from control and hypoxic groups are included in these graphs, including the aberrant 15% O₂ rat in which irANP was elevated. PaO₂ levels were similar between 8 and 10% O₂ groups, yet irANP and CRSA reached their highest levels in the 8% O₂ animals. The P values obtained from single regression analyses suggest that irANP was a better predictor of the CRSA response to hypoxia. Furthermore, when both factors were analyzed simulta-

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**Fig. 1.** Effects of room air (control) and graded hypoxic gas ventilation of anesthetized rats on extravasation of tracer albumin [131I-rat serum albumin (RSA) clearance (CRSA)] into various tissues. Clearances were measured over last 30 min of a 50-min period of gas treatment. Tissues are arranged in increasing order of control clearances. R, right; L, left; Visc, visceral; Ab, abdominal; Lat Gas, lateral gastrocnemius; Bk, back. *Significantly different from control, P ≤ 0.05.
neously by multiple regression, irANP alone (at constant PaO$_2$) was a significant factor in the C$_{RSA}$ response to hypoxia, whereas PaO$_2$ was not. In comparison, the decreases in C$_{RSA}$ observed in back skin and testis were not as strongly related to either irANP (P = 0.06 for both tissues) or PaO$_2$ (P > 0.5) when both factors were included in the regression analysis.

The tissues specificity of the C$_{RSA}$ response to hypoxia in this study was strikingly similar to previous observations in rats given exogenous ANP (18, 22, 24). In our own experiments (18), infusion of synthetic ANP (400 ng·kg$^{-1}$·min$^{-1}$) in rats given supplemental fluids to maintain PV increased clearance of $^{131}$I-BSA into gastrointestinal tissues (2.9–4.6-fold), kidney (2-fold), fat (1.9-fold), skeletal muscles (1.6-fold) and left ventricle (1.5-fold) but not in skin or lungs (brain and testis were not sampled). However, the magnitude of C$_{RSA}$ response for a given increment in irANP was greater in these previous experiments, particularly for gastrointestinal tissues. Regression slope coefficients relating C$_{RSA}$ to log irANP obtained in normovolemic rats given variable doses of ANP have been included in Fig. 2B (dashed lines) to illustrate this difference. [From Tucker et al. (18).]

PV and EVW. If elevated protein extravasation was a factor in the observed PV reductions during hypoxia, we would expect to find 1) a negative correlation between whole body C$_{RSA}$ and circulating PV and 2) a positive correlation between C$_{RSA}$ and water content of individual tissues. The former relationship is illustrated in Fig. 3, in which changes in PV during the clearance period are plotted as a function of whole body C$_{RSA}$, which was obtained by subtracting the $^{131}$I-RSA (35-min) distribution volume from the $^{125}$I-RSA (5-min) distribution volume. These data indicate that even though most of the hypoxia-induced PV reduction occurred before the clearance measurement (see Table 1), there was a definite linear relationship between decreases in PV and increments in C$_{RSA}$ during the clearance measurement period (P = 0.0001, r$^2$ = 0.7132).

Small-vessel PV, measured at the termination of the experiment as the tissue $^{125}$I-RSA (5-min) distribution
volume, and tissue EVW content evaluated by desiccation of the tissue samples are recorded in Table 2 for each treatment group. In testis, PV in rats ventilated with 10 or 8% O2 were significantly lower than in controls. For back skin and left ventricle, average PV were not different between groups by mean comparisons; however, linear-regression analyses indicated significant positive correlations between PV and the fraction of inspired O2, suggesting that hypoxia decreased PV in these tissues as well. Differences in EVV between control and hypoxia groups were insignificant for most tissues, including several of the tissues where CRSA was elevated. The jejunum, cecum, and colon all exhibited a trend toward lower EVV with increasing severity of hypoxia, and mean EVV in 8% O2 rats was significantly decreased in both jejunum (~10%) and colon (~13%) compared with that in controls. Of all the tissues with elevated CRSA during hypoxia, increased EVV was manifest only in the kidney. Water content was also increased in the left ventricle and right cerebrum; however, these changes appeared to be unrelated to changes in CRSA.

**DISCUSSION**

In the companion paper (1), it was shown that plasma ANP levels were more closely related to the fraction of inspired O2 (“alveolar hypoxia”) than to PO2 in arterial blood (“arterial hypoxemia”). This distinction allows us to evaluate the contribution of these factors to the observed changes in blood-to-tissue albumin transport. In tissues where increased CRSA was observed, these changes were better explained by elevations in plasma irANP as opposed to decrements in PAO2. The increases in CRSA were greater in 8% O2-treated animals, which had higher irANP levels, even though average PAO2 values were not different from animals ventilated with 10% O2.

Although changes in irANP and CRSA during hypoxia were clearly related, some of the tissues (most notably the jejunum and ileum) responded in a weaker manner compared with our own studies in nonhypoxic rats infused with exogenous ANP (see Fig. 2). It seems reasonable to attribute this decreased sensitivity to known compensatory hormonal and hemodynamic changes produced by hypoxia. Increases in plasma vasopressin (12), sympathoadrenal activity (9), and chemoreceptor stimulation (13) during hypoxic ventilation could decrease microvascular pressures and/or surface area for exchange via selective vasoconstriction of peripheral tissues. Other investigators (23) reported selective gastrointestinal vasoconstriction in dogs given intravenous ANP in the presence of autonomic blockade. Thus it is possible that decreases in jejunum, cecum, and colon EVV observed in the present study resulted from ANP-mediated vasoconstriction. Hypoxia-induced reductions in tissue perfusion were also sug-

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**Table 2. Tissue PV and EVW during normoxic and hypoxic ventilation**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>PV, µl/g</th>
<th>EVW, µl/g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room Air</td>
<td>15% O2</td>
</tr>
<tr>
<td>Visceral fat</td>
<td>11.2 ± 1.4</td>
<td>10.9 ± 1.2</td>
</tr>
<tr>
<td>Abdominal muscle</td>
<td>16.9 ± 1.6</td>
<td>17.3 ± 2.6</td>
</tr>
<tr>
<td>Lateral gastrocnemius</td>
<td>24.9 ± 1.7</td>
<td>23.3 ± 2.0</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>46.6 ± 3.8</td>
<td>42.5 ± 7.9</td>
</tr>
<tr>
<td>Right cerebrum</td>
<td>31.1 ± 4.0</td>
<td>31.8 ± 3.8</td>
</tr>
<tr>
<td>Back skin</td>
<td>17.1 ± 2.5</td>
<td>15.1 ± 1.9</td>
</tr>
<tr>
<td>Colon</td>
<td>64.1 ± 6.8</td>
<td>59.9 ± 5.1</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>301 ± 15</td>
<td>329 ± 25</td>
</tr>
<tr>
<td>Ileum</td>
<td>74.0 ± 4.4</td>
<td>62.5 ± 5.5</td>
</tr>
<tr>
<td>Cecum</td>
<td>89.5 ± 6.2</td>
<td>84.8 ± 6.1</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>186 ± 10</td>
<td>181 ± 19</td>
</tr>
<tr>
<td>Jejunum</td>
<td>89.8 ± 10.0</td>
<td>82.9 ± 7.4</td>
</tr>
<tr>
<td>Testis</td>
<td>45.9 ± 1.3</td>
<td>39.3 ± 4.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>570 ± 29</td>
<td>535 ± 35</td>
</tr>
<tr>
<td>Lungs</td>
<td>876 ± 92</td>
<td>1,010 ± 87</td>
</tr>
</tbody>
</table>

Values are means ± SE. n. No. of rats; EVW, extravascular water. PV are 125I-RSA 5-min distribution volumes normalized to body wt (g). EVW values are expressed as volume per gram tissue blood-free dry weight. PV and EVW were measured after 50 min of room air or hypoxic ventilation. *Significantly different from room air, P < 0.05. †Significant linear trend shown by regression analysis relative to level of hypoxia, P ≤ 0.05.
gested by our observation of significantly lower CRSA and tissue PV values in tissues previously found to be "ANP insensitive" (e.g., back skin). Furthermore, the presence of factors that blunt the action of released ANP on albumin and fluid extravasation in the hypoxic state could explain the leveling off of PV reduction and hematocrit increase after their initial changes in the rats exposed to 8 and 10% O2. In hypoxic states where tissue perfusion and hydrostatic are better maintained (i.e., in conscious models), elevated CRSA would likely have a proportionally greater effect on PV redistribution into extravascular spaces.

Transfer of protein from the circulation to the interstitial compartment acts to augment transfer of fluid volume, potentiating the loss of PV and accumulation of interstitial fluid (16). Of what advantage to a hypoxic animal is increased extravasation of fluid and protein? Loss of circulating PV could certainly be considered detrimental to systemic circulatory function at a time when increased blood supply is needed to compensate for decreased arterial O2 content. However, there is considerable evidence that hypoxia-induced ANP release benefits cardiopulmonary function by reducing hypoxia-induced pulmonary hypertension (3, 8, 10). The antihypertensive action of ANP on the pulmonary circulation could occur directly, by relaxing pulmonary arterioles (7), or indirectly, by reducing cardiac output in the face of increased pulmonary vascular resistance (11, 19). The relationship between iANP and CRSA observed in the present study suggests that an additional effect of ANP could be to reduce cardiac output and filling pressures by increasing microvascular fluid filtration in peripheral tissues. In contrast to the minimal diuresis observed in our hypotensive pentobarbital sodium-anesthetized rats, renal excretory function is usually enhanced during acute hypoxia in conscious humans and animals (5). Under these conditions, a transvascular shift of protein into peripheral tissues would have the important consequence of minimizing the rise in plasma colloid osmotic pressure during diuresis, thus favoring PV reduction over the loss of interstitial fluid.

In humans exposed to 3–5 h of a simulated altitude of 4,500 m (PO2 =40 Torr), Parving (14) observed a small increase in the transcapillary escape rate of 131I-albumin from 5.6 to 6.5%, which did not reach statistical significance. This led to the conclusion that increased albumin extravasation was unlikely to have contributed to the 7% reduction in PV observed in these subjects. Average increases in whole body CRSA in hypoxia groups were also small and insignificant in the present study. However, a negative relationship between whole body CRSA and circulating PV was clearly evident and statistically significant (Fig. 3). This finding suggests that on a whole body basis, the albumin extravasation rate is an insensitive index to changes in the driving force for fluid filtration. This can be at least partially explained by the nonlinear osmotic properties of serum albumin, which dictate disproportionately larger deviations in osmotic pressure per unit change in albumin concentration. Another problem is that whole body extravasation is dominated by visceral tissues that comprise only a small fraction of the total extracellular fluid volume. Taking these factors into account, we conclude that the modest increases in local extravasation rates in the present study resulted in the observed redistribution of extracellular fluid.

The lack of a detectable increase in EVW in tissues where CRSA was elevated is not surprising for the following reasons. First, given that the total EVW is much larger than the plasma space, a PV loss of the magnitude observed in these experiments (≈15%) would have a relatively small impact on EVW, particularly if it were distributed over several tissues. Second, it is unlikely that either capillary hydrostatic pressures or exchange surface areas were static in these experiments. Hypoxic ventilation resulted in prominent hypotension in all groups and reduced cardiac output in rats ventilated with 8% O2 (see Ref. 1). Thus it is possible that decrements in capillary hydrostatic pressure and flow opposed increases in filtration induced by albumin extravasation. This might also explain why EVW decreased during hypoxia in most of the gastrointestinal samples. Interestingly, the change in EVW (ΔEVW) appeared to be inversely related to the magnitude of CRSA elevation (ΔCRSA) in these tissues, with ileum showing the smallest ΔEVW (ΔCRSA = 2.2-fold) and colon showing the largest ΔEVW (ΔCRSA = 1.3-fold). These data suggest that increases in CRSA antagonized absorptive forces in these tissues.

In light of the known permeability actions of ANP (6, 18, 24), it has been suggested that ANP contributes to hypoxia-induced pulmonary edema (4). In the present study, lung CRSA was unaffected by hypoxia, although EVW tended to increase in rats ventilated with 15 and 10% O2 (P = 0.09). The variability of EVW data was higher in the lungs than in other tissues; therefore, the possibility of a Type II error (i.e., the probability of failing to detect a real difference) cannot be ruled out. Interestingly, rats given 8% O2 (i.e., those with the greatest iANP response) had mean EVW values that were more similar to control. In this case, it is possible that a reduction in cardiac output, as was observed in a group of identically treated rats (1), could have contributed to a lower EVW via a reduction in pulmonary microvascular pressure. When regression analysis was performed on all data except those from the 8% O2 group, we found no significant correlation between average ANP levels and lung EVW (r2 = 0.12). Taken together, these observations do not support increased permeability as a mechanism linking ANP to pulmonary edema. However, given the high variability in lung EVW and the possibility that cardiac output was altered in the most severely hypoxic animals, a definitive relationship between ANP and lung fluid balance, whether it be positive or negative, cannot be ascertained from this study.

Increased pulmonary capillary transit time subsequent to reduction of cardiac output might favor uptake of O2 from alveolar gas (20). This is not likely to be of consequence under conditions where reductions of alveolar PO2 occur in the presence of normal alveolar mem-
Atrial natriuretic peptide in acute mountain sickness: ANP and albumin transport in hypoxia

8% O₂, plasma ANP concentrations were elevated, and in ANP-insensitive tissues (lungs, heart, skin). In individual muscle, visceral fat, kidney, jejunum, ileum) but not most sensitive to the action of exogenous ANP (abdominal muscle, visceral fat, kidney, jejunum, ileum) but not in ANP-insensitive tissues (lungs, heart, skin). In individual tissues, the increases in albumin transport showed significant correlation with plasma concentrations of iANP but less so with levels of PAO₂. A notable depression in iANP sensitivity compared with previously observed effects of exogenous ANP was attributed to systemic vasoconstriction in the hypoxic rats, with subsequent reduction of functional capillary surface area. Loss of protein into peripheral tissues was associated with reductions of circulating PV during acute hypoxia. In intestinal tissues, decreases in EVW during 8% O₂ were inversely related to the magnitude of C_RSA elevation. We conclude that ANP-induced protein extravasation antagonizes reabsorptive forces, thus favoring PV contraction during acute hypoxia. ANP-induced volume contraction could act in compensatory fashion by either improving arterial oxygenation or antagonizing pulmonary hypertension during acute hypoxia. Whether such a mechanism contributes importantly to the physiology or pathophysiology of hypoxia in the conscious state remains to be determined.

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