The Effect of Oxygen with Exercise on Atrial Natriuretic Peptide in Chronic Obstructive Lung Disease

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A recent study on stable, hypoxemic, COLD patients in which ANP was stimulated by LBPP demonstrated that in these individuals elevation of ANP does not exert a "normal" suppressing effect on the PRA-PA axis. Accordingly, we exercised ten comparable COLD patients, another maneuver known to stimulate ANP and to elicit cardiorespiratory responses substantially different from those observed with LBPP. Patients were studied breathing room air and on 40 percent O2 to determine whether the level of oxygenation would modify ANP secretion. Basal levels of ANP on room air were markedly elevated above controls (269 ± 65 SE vs 70 ± 20 pg/ml, p < 0.05); PRA (13.0 ± 5.4 ng/ml/90 min) and PA (8.6 ± 3.5 ng/100 ml) were elevated (>2 SD over control levels of 8.1 ± 1.3 and 2.6 ± 0.7) in 6/10 and 2/10 patients, respectively. During exercise while breathing O2, only ANP increased; PRA and PA remained unchanged when breathing air and O2. Comprehensive statistical analyses failed to demonstrate a negative relationship between ANP and PRA or ANP and PA. We conclude that in patients with advanced COLD, ANP response to moderate exercise is significantly affected by correction of hypoxemia. This effect may be mediated through changes in airway resistance and consequently cardiac filling pressure. Chest 1992; 101:341-44

In vitro and animal studies have shown that ANPs have multiple anti-PRA system actions, including reduction of PRA secretion and blockade of PA secretion. In normal humans, acute endogenous or exogenous increases in plasma ANP produce parallel decreases in PRA and PA, supporting the view that ANP suppresses the PRA-PA axis. We were unable to establish correlations of this nature in patients with hypoxemic, hypercapnic COLD in whom the renal hemodynamic and hormonal patterns typically include depression of effective renal plasma flow and elevation of plasma ANP, PRA, and PA. No suppressive effect of ANP on PRA-PA was demonstrable, even when we induced a significant stimulation of ANP release by application of LBPP.

Physical exercise and hypoxemia are both reported to modify secretion of ANP in COLD patients, and are stimuli which these patients encounter on a regular basis, unlike LBPP. We therefore designed a study to evaluate the effects of hypoxemia and its correction both at rest and during exercise on ANP secretion in COLD patients.

METHODS

The study population comprised ten male patients with moderately advanced COLD; their pertinent characteristics, including arterial blood gas values during O2 administration, are shown in Table 1. All volunteers signed written informed consent prior to initiation of the experiment. Inclusion criteria were: (1) presence of COLD by clinical and physiologic criteria; (2) no history, ECG, or radiologic abnormalities indicative of primary heart disease; (3) clinical stability by history, physical examination, and arterial blood gas values. At the time of the study, two of the patients had sacral or ankle edema or both. All studies were performed in the morning, following an overnight fast. No attempt was made to modify maintenance treatment regimens in preparation for the study. These included the following: theophylline (three patients); beta, agonists (three patients); corticosteroids (three patients); furosemide (one patient); digoxin (one patient); nitroglycerin (one patient); and amiodarone (one patient).

Patients were kept in the supine position for the duration of the 4-h study. An indwelling heparin-lock catheter was inserted into a forearm vein for plasma ANP, PRA, and PA, all determined in

Table 1—Pertinent Characteristics of the Ten Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>61 ± 3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.63 ± 0.04</td>
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<tr>
<td>FEV₁ (L)</td>
<td>0.82 ± 0.09</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>40.2 ± 4.7</td>
</tr>
<tr>
<td>Pressure levels</td>
<td></td>
</tr>
<tr>
<td>Room air</td>
<td></td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>59 ± 4</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>50 ± 4</td>
</tr>
<tr>
<td>pH</td>
<td>7.37 ± 0.01</td>
</tr>
<tr>
<td>40% O₂</td>
<td></td>
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<tr>
<td>PaO₂ (mm Hg)</td>
<td>123 ± 10</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>53 ± 5</td>
</tr>
<tr>
<td>pH</td>
<td>7.35 ± 0.01</td>
</tr>
</tbody>
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*Values expressed as means ± SE.
breathed room air first and five patients breathed 40 percent O₂ first. Two exercise tests (supine position, 35 W for 3 min) were performed, at hours 1 and 3. Arterial blood gas values were measured just before each exercise bout. Hormonal, ventilatory, and hemodynamic measurements were made just before and at the end of exercise.

Statistical analyses utilized repeated measures ANOVA to determine if variables changed across time or as a function of condition. The level of significance was set at p<0.05. Significant F tests were followed by Newman-Keuls tests to identify the exact points of difference. All data are presented as means ± SE. Due to the nonnormal distribution pattern of PRA and PA, a square root transformation was performed before statistical analysis. This adjustment was successful in causing the data to be normally distributed. The PRA and PA values reported in the text are measured values.

RESULTS

During room air breathing at rest, plasma ANP was elevated when compared with the normal range for our laboratory of 70 ± 20 pg/ml for age-matched individuals; plasma ANP levels were not affected by exercise with subjects breathing room air (Fig 1). In contrast, during O₂ breathing the ANP levels, which at rest were not different from those measured with subjects breathing ambient air, increased (p<0.01) with exercise (Fig 1).

In the basal state, PRA was elevated (>2 SD) in six of ten and PA was elevated in two of ten subjects (control values for PRA and PA in a group of seven age-matched normal subjects were 2.6 ± 0.7 ng/ml/90 min and 8.1 ± 1.3 ng/100 ml, respectively); neither PRA nor PA was affected by exercise or by O₂ (Fig 1). No inverse ANP/PRA or ANP/PA correlation could be elicited, even when data were analyzed as maximal deflection points.

Basal and exercise VT, RR, VE, CO, HR, SV, VO₂, C(a-v)O₂, and C(a-v)O₃ were equivalent when subjects were breathing air and O₂ with the exception of the exercise RR and VE, which were lower when subjects were breathing O₂ (Table 2).

DISCUSSION

The ANP elevation in the basal state was similar to

Table 2—Physiologic Responses to Exercise with Subjects Breathing Air and 40 Percent O₂

<table>
<thead>
<tr>
<th></th>
<th>O₂ Breathing</th>
<th>p Value 1</th>
<th>p Value 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1</td>
<td>(2</td>
<td>(3</td>
</tr>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
</tr>
<tr>
<td>VT (ml)</td>
<td>411 ± 37</td>
<td>531 ± 51</td>
<td>365 ± 52</td>
</tr>
<tr>
<td>RR (breaths per min)</td>
<td>19 ± 2</td>
<td>29 ± 2</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>7.8 ± 0.5</td>
<td>15.4 ± 0.6</td>
<td>7.5 ± 0.6</td>
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<tr>
<td>CO (L/min)</td>
<td>4.9 ± 0.3</td>
<td>8.3 ± 0.4</td>
<td>4.4 ± 0.3</td>
</tr>
<tr>
<td>HR (beats per minute)</td>
<td>86 ± 6</td>
<td>107 ± 7</td>
<td>79 ± 4</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>59 ± 4</td>
<td>81 ± 6</td>
<td>58 ± 6</td>
</tr>
<tr>
<td>VO₂ (ml/min)</td>
<td>307 ± 28</td>
<td>484 ± 32</td>
<td>294 ± 32</td>
</tr>
<tr>
<td>C(a-v)O₂ (ml/L)</td>
<td>63 ± 6</td>
<td>104 ± 6</td>
<td>68 ± 9</td>
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</table>

*Values expressed as means ± SE.
that reported previously in COLD.\textsuperscript{10,11,13,16,20-31} When
patients breathed room air, exercise had no effect on
circulating ANP. Adnot et al\textsuperscript{13} and Piquet et al\textsuperscript{31}
observed a rise in ANP during exercise, but this
occurred only when the patients reached work rates
higher than 60 W. Our patients, quite similar to those
of Adnot et al\textsuperscript{13} and Piquet et al\textsuperscript{31} by clinical and
physiologic criteria, were only subjected to a 25-W
work rate. Thus, the results from the two laboratories
for patients breathing room air at rest and at moder-
ately low levels of exercise are comparable. Oxygen
breathing in our study had no effect on ANP in the
resting state, but during exercise it was associated
with a 20 percent increase in ANP over baseline.

The reason why moderate exercise increased ANP
only during O\textsubscript{2} breathing is not clear. It can be
speculated that O\textsubscript{2}, by decreasing airway resis-
tance,\textsuperscript{32,33} significantly reduced the magnitude of ele-
vation of ITP without much effect on RAP and thus
increased cardiac EFP (RAP minus ITP), a physiologic
parameter that currently is considered the major
modulator of ANP release.\textsuperscript{34,35} The observed lower RR
and $\text{V}E$, $\text{O}_2$ vs air, at comparable physical stress (same
work rate, exercise time and hemodynamic responses)
lends some support to this hypothesis.

The incidence of PRA-PA elevation in the basal state
was similar to that we previously reported in similar
patients;\textsuperscript{18} PRA and PA levels were not affected by $\text{O}_2$
or exercise. Even when acutely elevated, ANP showed
no suppressing effect on the PRA-PA axis. Lack of
suppression of PRA and PA by ANP in COLD patients
has now been demonstrated on at least two occasions
under different experimental conditions, LBPP and
exercise.

In patients with advanced COLD, circulating ANP
often is elevated two to three times above normal;\textsuperscript{8,26}
however, these patients commonly demonstrate
marked sodium and water retention. The most likely
explanation for this discrepancy is that the stimulatory
effect of inadequate renal perfusion on PRA and PA
secretion is more potent than the potential suppressive
effect of increased ANP on PRA and PA.\textsuperscript{9}

The clinical significance of the reciprocating con-
trols between ANP and the PRA-PA axis in the
regulation of sodium homeostasis is not entirely clear,
but a functional model has been proposed.\textsuperscript{37} In this
model, the major function of ANP appears to be the
protection against sodium and volume overload,
whereas the primary aim of the PRA-PA system
appears to be the defense of total body sodium. As a
corollary, the opposing action of ANP on PRA and PA
might be more important in the acute than in the
chronic regulation of total body sodium. In a situation
that involves an acute state of sodium excess, ANP
activity plays the important role of reducing cardiac
preload\textsuperscript{38} via multiple mechanisms, which may include
PRA and PA suppression. In a situation that involves
a state of chronic renal hypoperfusion, the PRA-PA
system plays the important role of supporting an
effective intravascular volume.\textsuperscript{36,30}

Previous studies have shown that in patients with
congestive heart failure, ANP has no suppressing effect
on PRA and PA, even at very high levels.\textsuperscript{9,10} Seemingly,
in this clinical state, ANP activity ceases to act as a
safety valve against the excessive activity of the PRA
system. The present study suggests that the same
considerations also apply to patients with COLD.

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