Synergistic Effects of Acute Hypoxemia and Hypercapnic Acidosis in Conscious Dogs
Renal Dysfunction and Activation of the Renin-Angiotensin System

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SUMMARY. The effects of acute hypoxemia and hypercapnic acidosis were examined in five unanesthetized dogs in which sodium intake was controlled at 80 mEq/24 hours for 4 days prior to study. Each animal was studied during combined acute hypoxemia and hypercapnic acidosis (Pao2 = 36 ± 1 mm Hg, Paco2 = 52 ± 1 mm Hg, pH = 7.18 ± 0.02), acute hypoxemia alone (Pao2 = 32 ± 1 mm Hg, Paco2 = 32 ± 1 mm Hg, pH = 7.34 ± 0.01), and acute hypercapnic acidosis alone (Pao2 = 82 ± 2 mm Hg, Paco2 = 51 ± 1 mm Hg, pH = 7.18 ± 0.02). Although mean arterial pressure, cardiac output, and heart rate increased during combined hypoxemia and hypercapnic acidosis, effective renal plasma flow and glomerular filtration rate decreased. In addition, filtered sodium load and urinary sodium excretion decreased during combined hypoxemia and hypercapnic acidosis. Either acute hypoxemia or hypercapnic acidosis alone resulted in increased mean arterial pressure, cardiac output, and heart rate. However, in contrast to their combined effects, renal hemodynamic function was unchanged and natriuresis was observed. Measurement of plasma renin activity and angiotensin II concentrations indicated that hypoxemia or hypercapnic acidosis alone resulted in moderate activation of the renin-angiotensin system. Moreover, combined hypoxemia and hypercapnic acidosis acted synergistically resulting in major renin-angiotensin activation. Systemic angiotensin II blockade using 1-sarcosine, 8-alanine, angiotensin II (2 µg/kg per min) during combined acute hypoxemia and hypercapnic acidosis resulted in decreased renal hemodynamic function. We conclude that acute hypoxemia and hypercapnic acidosis act synergistically to increase mean arterial pressure, diminish renal hemodynamic function, and activate the renin-angiotensin system. Systemic angiotensin inhibition studies suggest activation of the renin-angiotensin system maintains renal hemodynamic function during combined hypoxemia and hypercapnic acidosis, instead of mediating the renal vasoconstriction. (Circ Res 53: 202-213, 1983)

PATIENTS with respiratory failure frequently develop diminished renal function, including diminished renal plasma flow (Aber et al., 1963; Farber et al., 1977), diminished glomerular filtration rate (Daggett, 1977), diminished urinary sodium excretion (Kilburn and Dowell, 1971), and diminished free water excretion (White and Woodings, 1971). Although blood gas derangements are invariably present, their role in these renal abnormalities has remained unclear. In patients with respiratory failure, a correlation has been noted between hypoxemia/hypercapnia and renal dysfunction and edema. In 1960, Campbell and Short noted that the onset of CO2 retention heralded the appearance of edema in patients with chronic obstructive lung disease (Campbell and Short, 1960). Moreover, the combination of hypoxemia and hypercapnia in patients was correlated with diminished renal plasma flow (Aber et al., 1963; Farber et al., 1977) and increased plasma renin activity (Farber et al., 1977). However, interpretation of these clinical studies was difficult because of the presence of heart failure, chronic obstructive lung disease, and multiple medications.

Previous laboratory investigations have provided little insight into the role of blood gas derangements in abnormalities of renal function observed in clinical studies. Previous studies which have documented diminished renal function during acute hypoxemia or hypercapnic acidosis were performed in anesthetized, mechanically ventilated animals. To date, induction of moderate acute hypoxemia (Axelrod and Pitts, 1952; Ullman, 1961; Tuffley et al., 1970; Liang and Gavras, 1978; Anderson et al., 1980; Rose et al., 1982) in healthy human subjects or unanesthetized laboratory animals has been associated with impairment of renal function, despite activation of the renin-angiotensin system (Liang and Gavras, 1978; Anderson et al., 1980).
The effects of combined hypoxemia and hypercapnic acidosis on renal and cardiovascular function are poorly understood. Recently, combined acute hypoxemia and hypercapnic acidosis resulted in diminished renal blood flow in conscious dogs (Koehler et al., 1980). However, the impact on other aspects of renal function was not investigated. Thus, the physiological importance of blood gas derangements with regard to renal function has remained unclear.

To elucidate the effects of blood gas derangements on renal function, a study systematically evaluating the effects of single and combined blood gas derangements on renal function in unanesthetized animals is requisite. Therefore, the present investigation was undertaken to determine the effects of acute hypoxemia and hypercapnic acidosis separately and together on systemic and renal hemodynamic function, renal sodium excretion, and the renin-angiotensin system in unanesthetized animals in careful sodium balance.

Methods

Animal Preparation

Studies were performed on five unanesthetized female mongrel dogs weighing 19.4–27.4 kg. Surgical procedures performed at least 4 weeks prior to study, using pentobarbital anesthesia (30 mg/kg, iv) included: (1) exteriorization of the left carotid artery into a carotid loop for measurement of arterial pressure and sampling of arterial blood, (2) tracheostomy for monitoring and control of oxygen and carbon dioxide levels in respirable gas, and (3) splenectomy. Previous investigators have observed an increase in hematocrit during acute hypercapnic acidosis in unsplenectomized anesthetized dogs (Berns et al., 1979). Therefore, each animal was splenectomized to prevent possible increase in hematocrit or total blood volume during the acute blood gas derangements. Animals were excluded from study in the event of fever, infection at a surgical site, or inability to exercise normally.

Sodium balance was established with a palatable diet containing 5 mEq sodium/24 hours (Hill’s Prescription Diet h/d) and daily administration of 500 ml of 0.9% NaCl (75 mEq of sodium) by intravenous infusion given over 30 minutes. Constant sodium intake was maintained for 4 days prior to study, and a 24-hour urine collection was obtained from a stainless steel metabolic cage just before study to confirm the state of sodium balance. Before study, each animal was allowed free access to water, but food was withheld for approximately 18 hours.

Catheters inserted on the morning of study included an 18F bladder catheter (Travenol), percutaneous 18-gauge carotid loop catheter (Becton-Dickinson), and a central venous catheter (PE 160, Clay Adams) via percutaneous route through the right external jugular vein. Percutaneous catheters were inserted painlessly by prior intradermal lidocaine anesthesia. A tracheostomy tube (Portex 9.7 mm id) was inserted and secured, and the cuff was inflated in order to divert all respirable gas through the tube. After preparation, each animal was positioned for the study in a Pavlovian sling, and an infusion of D5W was begun at 0.5 ml/min containing concentrations of inulin and p-aminohippurate to establish and maintain blood levels between 15 and 20 mg/dl and 1–3 mg/dl, respectively. The tracheostomy tube was attached through a two-way Rudolph valve by corrugated plastic tubing so that ambient room air passed through the mixing chamber to the animal during inhalation. Exhaled gas exited through the Rudolph valve into the room.

Protocols (Table 1)

Effects of Acute Hypoxemia and Hypercapnic Acidosis in Intact Conscious Animals

The protocols were begun after 1 hour of equilibration in the sling, and after documentation of stable urine flow.

<table>
<thead>
<tr>
<th>Protocols</th>
<th>Control (0–80 min)</th>
<th>BGD1 (80–160 min)</th>
<th>BGD2 (160–200 min)</th>
<th>Post-control (240–260 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I HYPOX/com-</td>
<td>NORMOX</td>
<td>HYPOX</td>
<td>HYPOX + HC</td>
<td>NORMOX</td>
</tr>
<tr>
<td>bined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II HC/com-</td>
<td>NORMOCAP</td>
<td>HC</td>
<td>HC + HYPOX</td>
<td>NORMOCAP</td>
</tr>
<tr>
<td>combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III. HYPOX/alone</td>
<td>NORMOX</td>
<td>HYPOX1</td>
<td>HYPOX2</td>
<td>NORMOX</td>
</tr>
<tr>
<td>IV. HC/alone</td>
<td>NORMOCAP</td>
<td>HC1</td>
<td>HC2</td>
<td>NORMOCAP</td>
</tr>
<tr>
<td>V. Time-control</td>
<td>NORMOX</td>
<td>TC1</td>
<td>TC2</td>
<td>NORMOCAP</td>
</tr>
<tr>
<td>V. COMBINED + vehicle</td>
<td>NORMOCAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI. Combined</td>
<td>0–40 min</td>
<td>45–85 min</td>
<td>125–165 min</td>
<td></td>
</tr>
<tr>
<td>+ time-control</td>
<td>NORMOX</td>
<td>HYPOX &amp; HC</td>
<td>NORMOX</td>
<td></td>
</tr>
<tr>
<td>+ [Sar1, Ala1]-AII</td>
<td>NORMOCAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VII. COMBINED + [Sar1, Ala1]-AII</td>
<td>NORMOX</td>
<td>HYPOX &amp; HC</td>
<td>NORMOX</td>
<td></td>
</tr>
<tr>
<td>time-control</td>
<td>NORMOCAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIII. [Sar1, Ala1]-AII time-control</td>
<td>NORMOX</td>
<td>NORMOX</td>
<td>NORMOCAP</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HYPOX = acute hypoxemia, HC = acute hypercapnic acidosis, NORMOX = normoxia, NORMOCAP = normocapnia, TC = time-control.
The sequence of each protocol is outlined in Table 1. Measurements were obtained during four consecutive 20-minute control periods (C). Subsequently, the effects of acute hypoxemia alone or acute hypercapnia alone were determined during four consecutive 20-minute periods during the first blood gas derangement (BGD). This was followed by determination of the effects of combined acute hypoxemia and hypercapnia for two 20-minute periods during the second blood gas derangement (BGD). Post-control measurements were obtained during a 20-minute period, 40 minutes after cessation of the combined blood gas derangement. Each dog was studied on separate days in five protocols performed in random order at least 2 weeks apart.

Protocol I: Combined Acute Hypoxemia and Hypercapnia Preceded by Acute Hypoxemia. Following control measurements, acute hypoxemia (HYPOX) was induced in the first blood gas derangement period, followed by combined acute hypoxemia and hypercapnia (HYPOX + HC) in the second period.

Protocol II: Combined Acute Hypoxemia and Hypercapnia Preceded by Acute Hypercapnic Acidosis. The protocol was altered such that acute hypercapnic acidosis (HC) was induced during the first blood gas derangement period, followed by the combined derangement (HC + HYPOX).

Protocol III: Acute Hypoxemia Alone. Acute hypoxemia (HYPOX) was continued into the second blood gas derangement period (HYPOX) corresponding to the combined period in Protocol I. This allowed assessment of whether effects observed during the combined derangement were due to actual combination or increased duration of hypoxemia.

Protocol IV: Acute Hypercapnic Acidosis Alone. Acute hypercapnic acidosis (HC) was continued into the second blood gas derangement period (HC) corresponding to the combined period in Protocol II. This allowed assessment of effects of continuing hypercapnic acidosis compared to combined blood gas derangement.

Protocol V: Normoxemic, Normocapnic Time-Control. Effects of the protocol including infusions, drugs, and stress were controlled by precisely repeating the study in the absence of blood gas abnormalities on a separate day.

Effects of Combined Acute Hypoxemia and Hypercapnic Acidosis in Conscious Animals During Angiotensin II Inhibition Using 1-Sarcosine, 8-Alanine, Angiotensin II ([Sar, Ala]-All)

In order to assess the role of the renin-angiotensin system in the systemic and renal responses observed during combined acute hypoxemia and hypercapnic acidosis, each animal was studied in three additional protocols. Measurements were obtained during two consecutive 20-minute control periods (C), two consecutive 20-minute periods of combined acute hypoxemia and hypercapnic acidosis (combined HYPOX and HC) and two 20-minute post-control periods (PC) 40 minutes after cessation of combined HYPOX and HC (Table I). Each dog was studied on separate days in three protocols performed at least 2 weeks apart.

Protocol VI: Combined Acute Hypoxemia and Hypercapnic Acidosis During Infusion of Vehicle Alone. This protocol was performed to control for the effects of the angiotensin inhibitor vehicle in the present study and for a vasopressin inhibitor used in a different set of protocols reported in another study. Immediately following control measurements, infusion of the angiotensin inhibitor vehicle was begun, consisting of D5W at 0.5 ml/min. In addition, the vasopressin inhibitor vehicle was injected over 5 minutes which consisted of 0.53 ± 0.03 mEq (0.02 ± 0.002 mEq/kg) of the salt of acetic acid diluted in 20 ml D5W. This resulted in a calculated total [H+] administration of 6 nmol. The acetic acid vehicle was titrated to pH 6.5 using sodium hydroxide and pH meter (Corning 125) just before injection. After 5 minutes for injection of this vehicle and institution of the [Sar, Ala]-All vehicle (D5W), combined HYPOX and HC was instituted, and was continued with the vehicle infusion for 40 minutes. After completion of measurements during combined HYPOX and HC, 1000 ng of angiotensin I (Beckman Biochemicals) was injected intravenously to measure the systemic pressor response (18 ± 3 mm Hg) in the absence of angiotensin inhibition.

The combined blood gas derangement and vehicle were discontinued, and post-control measurements were then obtained 40 minutes later.

Protocol VII: Combined Acute Hypoxemia and Hypercapnic Acidosis with [Sar', Ala']-All Infusion. To assess the role of the renin-angiotensin system in effects observed during combined HYPOX and HC, Protocol VI was repeated except that [Sar', Ala']-All (U.S. Biochemicals) was infused in D5W at 2 µg/kg per min starting 5 minutes before, and through, combined HYPOX and HC. The vasopressin inhibitor vehicle was not administered. Infusion of the inhibitor was continued briefly after combined HYPOX and HC in order to assess the degree of inhibition of the systemic pressor response to an intravenous injection of 1000 ng of angiotensin I. With [Sar', Ala']-All infusion, the systemic pressor response to angiotensin I was reduced to −3 ± 3% of that observed in the intact state during Protocol VI.

Protocol VIII: [Sar', Ala']-All Infusion during Normoxemia and Normocapnia (n = 4). The agonist effects of [Sar, Ala']-All are well recognized (Johnson and Davis, 1973; Carey et al., 1978). To control for this potential action, Protocol VII was repeated with [Sar', Ala']-All infusion in D5W at 2 µg/kg per min in four dogs, except that the animals breathed room air throughout the entire protocol, and the vasopressin inhibitor vehicle was not administered. The systemic pressor response to 1000 ng of intravenous angiotensin I was reduced to −51 ± 29% of the response in Protocol VI.

Induction of Blood Gas Derangements

Acute hypoxemia was induced by adding 100% N2 to the inspired air via the mixing chamber until the end-tidal oxygen fraction (FEO2), measured by a fuel cell oxygen analyzer (Applied Technical Products), fell to 0.07. During the ensuing hyperpnea, hypocapnia was prevented by adding sufficient CO2 to the inspired air to maintain the FECO2 was 0.085. The ensuing hyperpnea, hypocapnia was prevented by adding sufficient CO2 to the inspired air to maintain the FECO2 was 0.085. During the ensuing hyperpnea, small amounts of 100% N2 were added to the end-tidal CO2 fraction (FECO2), measured by an infrared CO2 analyzer (Beckman LB-2), at the control level.

Acute hypercapnic acidosis was induced by adding 100% CO2 to the inspired air until the FCO2 was 0.085. During the resulting hyperpnea, small amounts of 100% N2 were added to the FCO2 at the control level, thus preventing hyperoxemia.

Combined acute hypoxemia and hypercapnia were induced by separately adding 100% N2 and CO2 to the inspired air (mixing chamber) until the FCO2 and FCO2 were 0.07 and 0.085, respectively.

Hemodynamic Measurements and Assays

Arterial pressure was measured from the carotid loop using a vascular transducer (Hewlett-Packard) zeroed 5 cm dorsal to the sternum in the upright animal. Cardiac
output was obtained by central venous injection of indo-
cyanine green dye with sampling of arterial blood through a
cuvette densitometer (Gilford 103IR). Total peripheral
resistance was calculated by dividing the mean arterial
pressure by the cardiac output.

Blood samples were obtained at the mid-point of each
20-minute urine collection period. Plasma and urine so-
dium and potassium were measured by flame photometry
(Instrumentation Laboratory 143) using lithium as an in-
ternal standard. Plasma and urine osmolality were mea-
sured by freezing point depression (Fiske OS Osmometer).
Plasma and urine inulin (Heyrovsky, 1956) and p-amino-
hippurate (Brun, 1951) were measured by spectrophotom-
etry, and renal clearances were used to estimate glomer-
ular filtration rate and effective renal plasma flow, re-
spectively. We have previously observed that renal p-amino-
hippurate extraction was unchanged in anesthetized ani-
mals during acute hypercapnic acidosis (Anderson et al.,
1980). Although p-aminohippurate extraction was not
measured during combined hypoxemia and hypercapnic
acidosis, the parallel decrease in glomerular filtration rate
and urinary sodium excretion indicated that changes in
extraction were unlikely.

Specimens for plasma renin activity and angiotensin II
assays were collected in EDTA, centrifuged at 4°C, and
stored at −80°C. Plasma renin activity was measured by
a radioimmunoassay technique (Sealey and Laragh, 1979).
Plasma angiotensin II concentrations were measured by a
modification of a previously described radioimmunoassay
technique (Freedlender and Goodfriend, 1979). The sam-
ple volume was increased by 70% with a water-washed
slurry of AG 50W-X2, hydrogen form (Bio-Rad Labora-
tories) instead of Fuller’s Earth and mixed for 60 minutes
on a rotator (20 rpm) at 4°C. This assay measured [des-
Asp’]-angiotensin II (angiotensin III), as well as angioten-
sin II.

Arterial blood gases were collected anaerobically and
analyzed within 30 minutes (BMS3, Radiometer). Hema-
tocrit was measured by the microhematocrit method (IEC
MB).

Data Analysis

Data were analyzed by 1- and 2-way analysis of vari-
ance (Steele and Torrie, 1960). Effects of blood gas de-
rangements were determined by comparison of blood gas
derangement periods to each other, and to the respective
control (protocol control) and post-control (protocol post-
control) periods for each protocol on the same day. In
addition, blood gas derangement periods were compared
to comparable periods performed on different days. Mul-
tiple comparisons were performed using Duncan’s multi-
ple range test (Steele and Torrie, 1960). Unless noted, it
can be considered that group comparisons were insignifi-
cant (P ≥ 0.05). In the text, all tables, and figures, variables
are expressed as the mean ± SE.

Results

Alterations in Arterial Blood Gases (Table 2)

Induction of acute blood gas derangements in the
conscious dogs resulted in moderate acute hypox-
emia and hypercapnic acidosis comitant with increased
minute ventilation (Table 2). Although arterial pH during
HYPOX + HC suggests an element of metabolic acidosis, calculated bicarbonate was unchanged. Moreover, arterial pH was compa-
rable (P = NS) during HYPOX + HC, compared with
HC + HYPOX periods in Protocols I and II.

Systemic Hemodynamic and Renal Effects of
Combined Acute Hypoxemia and Hypercapnic
Acidosis (Tables 3 and 4, Figs. 1-3)

Mean arterial pressure (Fig. 1) was increased (< 0.0005) during HYPOX + HC and HC + HYPOX, compared with the protocol control. Mean arterial pressure increased further (< 0.005) from the single blood gas derangement during HYPOX + HC and HC + HYPOX in Protocols I and II, respectively. By way of contrast, mean arterial pressure was un-
changed from HYPOX, to HYPOX2 and from HC1
to HC2 during HYPOX alone and HC alone, respect-
ively. Comparison of responses in the second blood
gas derangement period revealed that HC + HYPOX
resulted in increased (< 0.05) mean arterial pres-
sure, compared with HC2, but mean arterial pressure
was unchanged during HYPOX + HC, compared with
HYPOX2. Heart rate and cardiac output (Table 3)
increased (< 0.05) during both combined HY-
POX + HC and HC + HYPOX. However, heart rate
fell (< 0.001) from HYPOX to HYPOX + HC. Total
peripheral resistance (Table 3) was diminished
(< 0.05) during HYPOX + HC, compared with
protocol control in Protocol I. Glomerular filtration rate (Fig. 2) and effective
renal plasma flow (Fig. 3) fell (< 0.005) during
HYPOX + HC and HC + HYPOX, compared with
protocol control and the preceding single blood gas
derangement. The decrease in effective renal plasma
flow during combined hypoxemia and hypercapnic
acidosis in Protocol I was accompanied by an in-
crease in renal vascular resistance. Renal vascular
resistance was unchanged from C of 28 ± 4 to 28 ±
dynes sec cm−5 × 103 during HYPOX, but in-
creased (< 0.05) to 144 ± 45 dynes sec cm−5 ×
103 during HYPOX + HC in Protocol I. However,
renal vascular resistance was unchanged from C of
23 ± 4 to 29 ± 3 × 103 and 54 ± 8 dynes sec cm−5 ×
103 during HC and HC + HYPOX, respectively,
in Protocol II.

Urinary sodium excretion (Table 4) was un-
changed during HYPOX + HC and HC + HYPOX
in Protocols I and II, compared with the respective
protocol controls. However, urinary sodium excre-
tion was diminished (< 0.05) during HYPOX + HC,
compared with HYPOX in Protocol I. Although
fractional sodium reabsorption was unchanged, fil-
tered sodium load fell (< 0.001) during HYPOX
+ HC and HC + HYPOX, compared with protocol
control and the preceding single blood gas derange-
ment.

Hematocrit was unchanged from control to the
preceding single derangement or the combined
blood gas derangement in Protocols I and II. How-
ever, a slight but significant (< 0.05) decrease in
hematocrit was observed in the post-control period,
which was 4 ± 1% in Protocol I and 3 ± 0.8% in
Protocol II.
Systemic Hemodynamic and Renal Effects of Acute Hypoxemia or Hypercapnic Acidosis Alone (Tables 3 and 4, Figs. 1-3)

Mean arterial pressure (Fig. 1), heart rate, and cardiac output (Table 3) increased (P < 0.05) during HYPOX alone and HC alone (HC). However, all systemic hemodynamic variables were unchanged during the normoxic, normocapnic time-control except for a slight increase in heart rate in the post-control period.

Glomerular filtration rate (Fig. 2), effective renal plasma flow (Fig. 3), and renal vascular resistance were unchanged during HYPOX alone and HC alone, compared with protocol control. However, effective renal plasma flow decreased (P < 0.05) from HYPOX to HYPOX2. Glomerular filtration rate and effective renal plasma flow were unchanged during the time-control.

Urinary sodium excretion (Table 4) increased (P < 0.05) during HYPOX alone and HC alone during HYPOX1 and HC1, respectively.

Hematocrit was unchanged from control to both hypoxic periods in Protocol III and both hyper-

![Image](http://circres.ahajournals.org/)

**FIGURE 1.** Mean arterial pressure increased during either acute hypoxemia (HYPOX) or acute hypercapnic acidosis (HC) and increased further during combined acute hypoxemia and hypercapnic acidosis.

* Represents comparison to protocol control period.
TABLE 3
Systemic Hemodynamic Function during Acute Hypoxemia and Hypercapnic Acidosis

<table>
<thead>
<tr>
<th>Protocols</th>
<th>Control (0-80 min)</th>
<th>BGD1 (80-160 min)</th>
<th>BGD2 (160-200 min)</th>
<th>Post-control (240-260 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. HYPOX/combined</td>
<td>NORMOX</td>
<td>HYPOX</td>
<td>HYPOX+HCP</td>
<td>NORMOX</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>88 ± 12</td>
<td>151 ± 5*</td>
<td>119 ± 5*</td>
<td>113 ± 9*</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>3.1 ± 0.5</td>
<td>5.0 ± 0.4*</td>
<td>4.7 ± 0.2*</td>
<td>3.2 ± 0.3</td>
</tr>
<tr>
<td>TPR (dynes sec cm^-5)</td>
<td>3297 ± 491</td>
<td>1837 ± 89*</td>
<td>2353 ± 167*</td>
<td>2828 ± 284</td>
</tr>
<tr>
<td>II. HC/combined</td>
<td>NORMOCAP</td>
<td>HC</td>
<td>HC+HYPOX</td>
<td>NORMOCAP</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>86 ± 10</td>
<td>125 ± 6*</td>
<td>131 ± 8*</td>
<td>96 ± 7</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>2.6 ± 0.2</td>
<td>3.9 ± 0.3*</td>
<td>4.0 ± 0.7*</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>TPR (dynes sec cm^-5)</td>
<td>3368 ± 244</td>
<td>2653 ± 211</td>
<td>3001 ± 365</td>
<td>3233 ± 366</td>
</tr>
<tr>
<td>III. HYPOX/alone</td>
<td>NORMOX</td>
<td>HYPOX</td>
<td>HYPOX</td>
<td>NORMOX</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>93 ± 7</td>
<td>161 ± 12*</td>
<td>145 ± 9*</td>
<td>121 ± 4*</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>3.9 ± 0.3</td>
<td>5.8 ± 0.4*</td>
<td>5.9 ± 0.5*</td>
<td>4.2 ± 0.2</td>
</tr>
<tr>
<td>TPR (dynes sec cm^-5)</td>
<td>2335 ± 265</td>
<td>1707 ± 149</td>
<td>1694 ± 163</td>
<td>2057 ± 99</td>
</tr>
<tr>
<td>IV. HC/alone</td>
<td>NORMOCAP</td>
<td>HC</td>
<td>HC</td>
<td>NORMOCAP</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>86 ± 10</td>
<td>133 ± 7*</td>
<td>129 ± 10*</td>
<td>104 ± 13*</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>2.7 ± 0.5</td>
<td>3.9 ± 0.8*</td>
<td>3.5 ± 0.7</td>
<td>3.0 ± 0.6</td>
</tr>
<tr>
<td>TPR (dynes sec cm^-5)</td>
<td>4248 ± 976</td>
<td>3393 ± 983*</td>
<td>3482 ± 871</td>
<td>4020 ± 1057</td>
</tr>
<tr>
<td>V. Time-control</td>
<td>NORMOCAP</td>
<td>TC1</td>
<td>TC2</td>
<td>NORMOCAP</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>88 ± 5</td>
<td>99 ± 4</td>
<td>96 ± 3</td>
<td>103 ± 13*</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>3.0 ± 0.1</td>
<td>3.2 ± 0.1</td>
<td>3.2 ± 0.2</td>
<td>3.0 ± 0.2</td>
</tr>
<tr>
<td>TPR (dynes sec cm^-5)</td>
<td>2893 ± 187</td>
<td>2776 ± 74</td>
<td>2828 ± 179</td>
<td>2837 ± 207</td>
</tr>
</tbody>
</table>

Abbreviations: HYPOX = acute hypoxemia, HC = acute hypercapnic acidosis, HR = heart rate, CO = cardiac output, TPR = total peripheral resistance.
* Denotes significant difference from protocol control value, P < 0.05.
† Denotes significant difference between BGD1 and BGD2, P < 0.05.

Renin-Angiotensin Activation during Acute Blood Gas Derangements (Figs. 4 and 5)

Plasma renin activity (Fig. 4) increased 12-fold (P < 0.0005) during HYPOX + HC, and 10-fold (P < 0.005) during HC + HYPOX, compared with protocol control. Plasma renin activity increased 5-fold during combined acute hypoxemia and hypercapnic acidosis but was unchanged during acute hypoxemia or acute hypercapnic acidosis alone. * Represents comparison to protocol control period.

![Figure 2](http://circres.ahajournals.org/)

**Figure 2.** Glomerular filtration rate decreased during combined acute hypoxemia and hypercapnic acidosis but was unchanged during acute hypoxemia or acute hypercapnic acidosis alone. * Represents comparison to protocol control period.

![Figure 3](http://circres.ahajournals.org/)

**Figure 3.** Effective renal plasma flow decreased during combined acute hypoxemia and hypercapnic acidosis but was unchanged during acute hypoxemia or hypercapnic acidosis alone compared to protocol control. * Represents comparison to protocol control period.
### TABLE 4
Renal Sodium Excretion during Acute Hypoxemia and Hypercapnic Acidosis

<table>
<thead>
<tr>
<th>Protocols</th>
<th>Control (0-80 min)</th>
<th>BGD$_1$ (80-160 min)</th>
<th>BGD$_2$ (160-200 min)</th>
<th>Post-control (240-260 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. HYPOX/combined</td>
<td>NORMOX</td>
<td>HYPOX</td>
<td>HYPOX+HC</td>
<td>NORMOX</td>
</tr>
<tr>
<td>(71 ± 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$U_Na$ V (µEq/min)</td>
<td>39 ± 10</td>
<td>74 ± 28</td>
<td>27 ± 8†</td>
<td>42 ± 18</td>
</tr>
<tr>
<td>$F_Na$ (µEq/min)</td>
<td>9030 ± 976</td>
<td>10214 ± 1699</td>
<td>5073 ± 1901†</td>
<td>11434 ± 2776*</td>
</tr>
<tr>
<td>FR</td>
<td>0.996 ± 0.001</td>
<td>0.993 ± 0.002</td>
<td>0.993 ± 0.002</td>
<td>0.996 ± 0.001</td>
</tr>
<tr>
<td>II. HC/combined</td>
<td>NORMOCAP</td>
<td>HC</td>
<td>HC+HYPOX</td>
<td>NORMOCAP</td>
</tr>
<tr>
<td>(98 ± 11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$U_Na$ V (µEq/min)</td>
<td>44 ± 10</td>
<td>67 ± 27</td>
<td>35 ± 11</td>
<td>27 ± 11</td>
</tr>
<tr>
<td>$F_Na$ (µEq/min)</td>
<td>10236 ± 603</td>
<td>9702 ± 536</td>
<td>6508 ± 922†</td>
<td>12194 ± 1233</td>
</tr>
<tr>
<td>FR</td>
<td>0.995 ± 0.001</td>
<td>0.994 ± 0.002</td>
<td>0.994 ± 0.002</td>
<td>0.997 ± 0.001</td>
</tr>
<tr>
<td>III. HYPOX/alone</td>
<td>NORMOCAP</td>
<td>HYPOX$_1$</td>
<td>HYPOX$_2$</td>
<td>NORMOCAP</td>
</tr>
<tr>
<td>(80 ± 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$U_Na$ V (µEq/min)</td>
<td>26 ± 19</td>
<td>133 ± 37*</td>
<td>83 ± 36†</td>
<td>49 ± 22</td>
</tr>
<tr>
<td>$F_Na$ (µEq/min)</td>
<td>7636 ± 732</td>
<td>8600 ± 764</td>
<td>8269 ± 583</td>
<td>7498 ± 1015</td>
</tr>
<tr>
<td>FR</td>
<td>0.995 ± 0.002</td>
<td>0.985 ± 0.004*</td>
<td>0.990 ± 0.004‡</td>
<td>0.992 ± 0.004‡</td>
</tr>
<tr>
<td>IV. HC/alone</td>
<td>NORMOCAP</td>
<td>HC</td>
<td>HC</td>
<td>NORMOCAP</td>
</tr>
<tr>
<td>(55 ± 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$U_Na$ V (µEq/min)</td>
<td>23 ± 10</td>
<td>90 ± 32*</td>
<td>81 ± 33*</td>
<td>32 ± 16</td>
</tr>
<tr>
<td>$F_Na$ (µEq/min)</td>
<td>7985 ± 652</td>
<td>8403 ± 236</td>
<td>9471 ± 1152</td>
<td>8404 ± 504</td>
</tr>
<tr>
<td>FR</td>
<td>0.997 ± 0.001</td>
<td>0.987 ± 0.004*</td>
<td>0.992 ± 0.004</td>
<td>0.996 ± 0.002</td>
</tr>
<tr>
<td>V. Time-control</td>
<td>NORMOCAP</td>
<td>TC$_1$</td>
<td>TC$_2$</td>
<td>NORMOCAP</td>
</tr>
<tr>
<td>(80 ± 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$U_Na$ V (µEq/min)</td>
<td>38 ± 8</td>
<td>34 ± 8</td>
<td>26 ± 8</td>
<td>29 ± 10</td>
</tr>
<tr>
<td>$F_Na$ (µEq/min)</td>
<td>8778 ± 709</td>
<td>9685 ± 304</td>
<td>10143 ± 411</td>
<td>8645 ± 1291</td>
</tr>
<tr>
<td>FR</td>
<td>0.995 ± 0.001</td>
<td>0.995 ± 0.001</td>
<td>0.997 ± 0.001</td>
<td>0.997 ± 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: HYPOX = acute hypoxemia, HC = acute hypercapnic acidosis, $U_Na$ V = urinary sodium excretion, $F_Na$ = filtered sodium load, FR = fractional sodium reabsorption.

* Denotes significant difference from protocol control value, $P < 0.05$.
† Denotes significant difference between BGD$_1$ and BGD$_2$, $P < 0.05$.
‡ Values in parentheses represent urinary sodium excretion, mEq 24/hr.

The severity of combined hypoxemia and hypercapnic acidosis and the degree of hyperpnea were comparable between protocols with vehicle alone or [Sar$_1$,Ala$_8$]-AngII infusion. Therefore the data were pooled. $P_{aO_2}$ decreased (P < 0.05) from C of 81 ± 2 to 36 ± 3 mm Hg during combined HYPOX and HC, and was 81 ± 3 mm Hg during the post-control period. $P_{aCO_2}$ and arterial pH were 7.40 ± 0.01 to 7.18 ± 0.01. $P_{aCO_2}$ and arterial pH were 28 ± 1 mm Hg and 7.40 ± 0.01, respectively in the post-control period. Minute ventilation increased (P < 0.05) from C of 4.1 ± 0.6 to 46.6 ± 5.1 liters/min during combined HYPOX and HC, and was 4.4 ± 1.0 liters/min in the post-control period.
Synergistic Effects of Acute Hypoxemia and Hypercapnic Acidosis


FIGURE 5. Combined acute hypoxemia and hypercapnic acidosis acted synergistically to increase plasma angiotensin II concentrations 6- to 9-fold, substantially above levels observed during hypoxemia or hypercapnic acidosis alone. * Represents comparison to protocol control period.

Control period. Thus, the severities of hypoxemia, hypercapnic acidosis, and hyperpnea in the angiotensin inhibition protocols were comparable to HYPOX + HC and HC + HYPOX periods in Protocols I and II.

Mean arterial pressure, heart rate and cardiac output increased during combined HYPOX and HC with vehicle alone (Table 5). Mean arterial pressure increased but changes in heart rate and cardiac output were not statistically significant during combined HYPOX and HC with [Sar²,Ala⁸]-AII. The magnitude of the systemic pressor response during combined HYPOX and HC with [Sar²,Ala⁸]-AII appeared to be less than during combined HYPOX and HC with vehicle alone with a change of 13 ± 4 vs. 21 ± 4 mm Hg, respectively. However, these systemic pressor responses were not statistically different. In addition, total peripheral resistance fell during combined HYPOX and HC with vehicle alone, but was unchanged during combined HYPOX and HC with [Sar²,Ala⁸]-AII.

Glomerular filtration rate and effective renal plasma flow were unchanged during combined HYPOX and HC with vehicle alone, but fell during the combined HYPOX and HC with [Sar²,Ala⁸]-AII (Table 6).

Renal vascular resistance was unchanged from C of 26 ± 3 to 89 ± 41 dynes sec cm⁻⁵ x 10⁻³ during combined HYPOX and HC with vehicle alone, and the increase from C of 29 ± 2 to 190 ± 82 dynes sec cm⁻⁵ x 10⁻³ during combined HYPOX and HC with

<table>
<thead>
<tr>
<th>TABLE 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Hemodynamic Function during Combined Acute Hypoxemia and Hypercapnic Acidosis with Angiotensin II Inhibition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protocols</th>
<th>Control (0-40 min)</th>
<th>Combined HYPOX and HC (45-85 min)</th>
<th>Post-control (125-145 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI. Intact (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>118 ± 6</td>
<td>139 ± 6*</td>
<td>115 ± 6</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>91 ± 12</td>
<td>131 ± 4*</td>
<td>97 ± 12</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>2.6 ± 0.3</td>
<td>4.6 ± 0.3*</td>
<td>3.0 ± 0.2</td>
</tr>
<tr>
<td>TPR (dynes sec cm⁻⁵)</td>
<td>3852 ± 317</td>
<td>2475 ± 137*</td>
<td>3219 ± 220</td>
</tr>
<tr>
<td>VII. [Sar²,Ala⁸]-AII (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>118 ± 4</td>
<td>131 ± 6*</td>
<td>117 ± 4</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>98 ± 11</td>
<td>125 ± 10</td>
<td>97 ± 6</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>2.7 ± 0.1</td>
<td>4.2 ± 0.7</td>
<td>3.0 ± 0.3</td>
</tr>
<tr>
<td>TPR (dynes sec cm⁻⁵)</td>
<td>3880 ± 397</td>
<td>2912 ± 717</td>
<td>3394 ± 438</td>
</tr>
<tr>
<td>VIII. [Sar²,Ala⁸]-AII time-control (n = 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>105 ± 7</td>
<td>105 ± 8</td>
<td>114 ± 5</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>83 ± 12</td>
<td>85 ± 24</td>
<td>101 ± 18</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>2.8 ± 0.3</td>
<td>2.6 ± 0.3</td>
<td>3.7 ± 0.1*</td>
</tr>
<tr>
<td>TPR (dynes sec cm⁻⁵)</td>
<td>3538 ± 469</td>
<td>3413 ± 515</td>
<td>2531 ± 72</td>
</tr>
</tbody>
</table>

Abbreviations: combined HYPOX and HC = combined acute hypoxemia and hypercapnic acidosis, MAP = mean arterial pressure, HR = heart rate, CO = cardiac output, TPR = total peripheral resistance.

* Denotes significant difference from protocol control values, P < 0.05.
Renal Hemodynamic Effects of Combined Acute Hypoxemia and Hypercapnic Acidosis during Angiotensin II Inhibition

<table>
<thead>
<tr>
<th>Protocols</th>
<th>Control (0–40 min)</th>
<th>Combined HYPOX and HC (45–85 min)</th>
<th>Post-control (125–145 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI. Intact (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>57 ± 7</td>
<td>42 ± 11</td>
<td>78 ± 8</td>
</tr>
<tr>
<td>ERPF (ml/min)</td>
<td>234 ± 38</td>
<td>190 ± 55</td>
<td>306 ± 38</td>
</tr>
<tr>
<td>VII. [Sar1, Ala8]-AII (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>57 ± 4</td>
<td>24 ± 6*</td>
<td>50 ± 11</td>
</tr>
<tr>
<td>ERPF (ml/min)</td>
<td>217 ± 14</td>
<td>95 ± 34*</td>
<td>242 ± 22</td>
</tr>
<tr>
<td>VIII. [Sar1, Ala8]-AII time-control (n = 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>51 ± 5</td>
<td>59 ± 3</td>
<td>60 ± 5</td>
</tr>
<tr>
<td>ERPF (ml/min)</td>
<td>237 ± 34</td>
<td>282 ± 60</td>
<td>245 ± 27</td>
</tr>
</tbody>
</table>

**Abbreviations:** Combined HYPOX and HC = combined acute hypoxemia and hypercapnic acidosis. GFR = glomerular filtration rate. ERPF = effective renal plasma flow. * Denotes significant difference from protocol control values, P < 0.05.

**Effects of [Sar1, Ala8]-AII Infusion during Normoxemia and Normocapnia (n = 4).**

Control PaO2 and PacO2 of 83 ± 2 and 31 ± 1 mm Hg, respectively, were unchanged during the subsequent administration of [Sar1, Ala8]-AII or during the post-control periods. Arterial pH was also unchanged from control of 7.40 ± 0.01. Minute ventilation was unchanged from control of 2.8 ± 0.2 liters/min.

Systemic (Table 5) and renal hemodynamic function (Table 6) were unchanged with the administration of [Sar1, Ala8]-AII during this control except for an unexplained increase in cardiac output in the post-control period. Renal vascular resistance was unchanged from C of 54 ± 22 to 35 ± 8 dyne sec cm⁻⁵ × 10³ with [Sar1, Ala8]-AII infusion in the time-control. Urinary sodium excretion and hematocrit were also unchanged in the [Sar1, Ala8]-AII time-control.

**Discussion**

The present study clearly demonstrates that, in contrast to their separate effects, acute hypoxemia and hypercapnic acidosis act synergistically in unanesthetized dogs to diminish renal hemodynamic function and urinary sodium excretion concomitant with substantial activation of the renin-angiotensin system.

This study was undertaken because of conflicting results among previous laboratory investigations which assessed the effects of acute hypoxemia or hypercapnic acidosis on renal function. The main discrepancy between previous studies appears to be related to employment of barbiturates, positive pressure ventilation, and neuromuscular paralysis. Barbiturate anesthesia (Burger et al., 1976) and positive pressure ventilation (Bark et al., 1980) may themselves activate the renin-angiotensin system and/or diminish renal blood flow.

Thus, in contrast to previous investigations in anesthetized animals, unanesthetized animal and human studies have observed no impairment of renal function during acute hypoxemia (Toth, 1937; Lewis et al., 1942; Berger et al., 1949; Axelrod and Pitts, 1952; Ferguson and Smith, 1953; Ullman, 1961; Walker, 1982) and acute hypercapnic acidosis (Barbour et al., 1953; Anderson et al., 1980; Rose et al., 1982). The systemic pressor and natriuretic responses during acute hypoxemia or hypercapnic acidosis in the present study are in agreement with these previous studies in unanesthetized animals.

The effects of combined hypoxemia and hypercapnic acidosis on renal function were evaluated because of previous clinical studies which observed that abnormalities in renal hemodynamic function were associated with hypercapnia and hypoxemia in contrast to hypoxemia alone (Aber et al., 1963; Farber et al., 1977). Moreover, Weissman et al. (1976) observed increased renal vascular resistance
Ala8]-AII has been previously documented in vitro competitive antagonism of angiotensin II by [Sar1, Ala8]-AII. The compound [Sar1, Ala8]-AN, possessing only slight agonist activity (Johnson and Davis, 1973), was used in vitro and in vivo in anesthetized and conscious animals. Using rabbit aortic strips, and in vivo in anesthetized and conscious animals, Ala8]-AII antagonized previously.

The major renal effect of the combined gas derangement in the present study appears to be upon hemodynamic function resulting in diminished delivery of water and electrolytes to the proximal tubule. Further support for this hypothesis is that impaired sodium excretion was associated with diminished filtered sodium load. If the study had been conducted under conditions of a lower fractional reabsorption of sodium, then increased tubular reabsorption may have been demonstrable, as well as diminished filtered sodium load.

Several possible mechanisms may have contributed to the diminished renal hemodynamic function during hypoxemia and hypercapnic acidosis, including the renin-angiotensin system, sympathetic nervous system, and vasopressin. The renin-angiotensin system was considered a likely mediator of diminished renal hemodynamic function during combined acute hypoxemia and hypercapnic acidosis in view of the striking increase in circulating angiotensin II, and previous observations that peripheral angiotensin II infusion at 25 ng/kg per min resulted in diminished renal plasma flow and glomerular filtration rate (Healey et al., 1965).

The increase in plasma renin activity (Liang and Gavras, 1978) and circulating angiotensin II (Zakhem et al., 1976) during acute hypoxemia has been observed in previous laboratory investigations in unanesthetized animals. In addition, the rise in plasma renin activity during acute hypercapnic acidosis in conscious dogs has been reported previously (Rose et al., 1982). However, the synergistic effect of combined hypoxemia and hypercapnic acidosis in renin-angiotensin activation has not been recognized previously.

In order to assess the role of the renin-angiotensin in diminished renal hemodynamic function, a competitive angiotensin antagonist was employed. Although possessing considerable affinity for and binding with angiotensin II receptors, the angiotensin II analog [Sar1, Ala8]-All possesses only slight agonist activity (Johnson and Davis, 1973). The competitive antagonism of angiotensin II by [Sar1, Ala8]-All has been previously documented in vitro using rabbit aortic strips, and in vivo in anesthetized rats (Pals et al., 1971). We chose the dosage of [Sar1, Ala8]-All of 2.0 μg/kg per min intravenously in view of previous observations (Levens et al., 1983). These investigators observed that intra-renal administration of [Sar1, Ala8]-All at 2.5 μg/kg per min resulted in spillover into the systemic circulation with over 80% reduction of the systemic pressor response to angiotensin I within 10 minutes.

The effects of angiotensin II inhibition during combined hypoxemia and hypercapnic acidosis in the present study suggest angiotensin II is not the sole mediator of the systemic pressor response since mean arterial pressure increased during the combined derangement with [Sar1, Ala8]-All. Unexpectedly, angiotensin blockade with [Sar1, Ala8]-All failed to increase renal hemodynamic function during combined hypoxemia and hypercapnic acidosis. In fact, renal hemodynamic function worsened, and renal vascular resistance increased. Thus, systemic angiotensin blockade resulted in diminished renal hemodynamic function, rather than improvement.

There are several interpretations for diminished renal hemodynamic function with angiotensin II inhibition during combined hypoxemia and hypercapnic acidosis. They include an agonist effect of [Sar1, Ala8]-All, inadequate angiotensin II blockade, diminished responsiveness of the renal vasculature to angiotensin II, and a protective role of angiotensin II on renal hemodynamic function. The possibility of an agonistic action of [Sar1, Ala8]-All (Johnson and Davis, 1973; Carey et al., 1978) is unlikely, since systemic and renal hemodynamic function were unchanged with [Sar1, Ala8]-All administration during normoxemia and normocapnia. Inadequate angiotensin II blockade is unlikely in view of the abrogation of the systemic pressor response to angiotensin I by the inhibitor. In addition, if the underlying phenomenon were inadequate angiotensin II blockade, one would expect that renal hemodynamic function during combined HYPOX and HC with [Sar1, Ala8]-All would be identical to unchanged renal hemodynamic function during combined HYPOX and HC with vehicle. Diminished renal vascular responsiveness to angiotensin II during combined hypoxemia and hypercapnic acidosis is also not an attractive possibility. If the renin-angiotensin system was substantially activated with minimal effect on the systemic or renal circulations because of diminished responsiveness, addition of an inhibitor of angiotensin II should have minimal effect.

The findings in the present study are most consistent with the hypothesis that angiotensin II maintained renal hemodynamic function during combined hypoxemia and hypercapnic acidosis. This effect could have been exerted through either systemic hemodynamic changes, or direct effects on the renal vasculature. The rise in mean arterial pressure during combined hypoxemia and hypercapnic acidosis with [Sar1, Ala8]-All in the present study was comparable to vehicle alone. Because renal perfu-
sion pressure was not measured in the present study, we cannot be absolutely sure that it was comparable between the angiotensin II inhibition and intact (vehicle alone) protocols. However, the similarity of the systemic pressor responses suggests that alteration of renal perfusion pressure was not responsible for diminished renal hemodynamic function with angiotensin II blockade. The alternate hypothesis is that angiotensin II maintained renal hemodynamic function through effects on the renal circulation. This possibility is supported by previous observations that angiotensin II is important in renal autoregulation during aortic constriction and diminished renal perfusion pressure in sodium-depleted anesthetized dogs (Hall et al., 1981). These investigators observed that glomerular filtration rate was maintained during aortic constriction and decreased renal perfusion pressure in intact dogs. However, in the presence of angiotensin II blockade using the angiotensin I-converting enzyme inhibitor SQ14,225, comparable aortic constriction and reduction in renal perfusion resulted in diminished glomerular filtration rate and calculated efferent arteriolar resistance. Additional support for a selective effect of angiotensin II on the efferent renal arteriole can be found in a recent study assessing the effects of angiotensin II on isolated rabbit kidney afferent and efferent arterioles (Edwards, 1983). Both types of vessels responded to norepinephrine, but only the efferent arteriole contracted with angiotensin II. These studies suggest angiotensin II may maintain glomerular filtration rate by acting preferentially on the efferent arteriole. Whereas renal blood flow was dissociated from the fall in glomerular filtration rate during aortic constriction with angiotensin II inhibition (Hall, et al., 1981), effective renal plasma flow fell in parallel with glomerular filtration rate during hypoxemia and hypercapnic acidosis with angiotensin inhibition in the present study. Despite this dissimilarity, one explanation for the findings in the present study is that activation of the renin-angiotensin system maintains glomerular filtration rate during hypoxemia and hypercapnic acidosis through an effect on the efferent arteriole.

Other non-angiotensin factors may have mediated the renal vasoconstriction during hypoxemia and hypercapnic acidosis, including increased α-adrenergic activity or increased circulating vasopressin. The observation that sinoaortic denervation abrogates the renal vasoconstriction during combined hypoxemia and hypercapnic acidosis suggests a role for the sympathetic nervous system (Koehler et al., 1980). In addition, it is possible that angiotensin II inhibition in the present study may have enhanced the renal vasoconstriction from alternate systems including the α-adrenergic nervous system. Unfortunately, we have no direct information on these points, and future studies are needed to assess these possibilities.

Several possible explanations may be considered for the disparity between the diminished renal hemodynamic function with combined hypercapnic acidosis with preceding hypoxemia or hypercapnic acidosis in Protocols I and II vs. unchanged renal hemodynamic function with the combined derangement without preceding derangement in Protocol VI. It certainly is possible that 80 minutes of hypoxemia or hypercapnic acidosis contributed to changes that led to renal vasoconstriction upon induction of the combined derangement. The mechanism by which renal vasoconstriction may have been enhanced by the preceding derangement is unclear, but it very likely does not involve the renin-angiotensin system, in view of the suggestion from the angiotensin inhibition protocols that angiotensin II maintains rather than diminishes renal hemodynamic function. We considered the possibility that the acetate/acetic acid vehicle used for the vasopressin antagonist in Protocol VI as part of another study may have abolished the renal vasoconstriction during hypoxemia or hypercapnic acidosis. This is unlikely because of the minute amount administered, and the evidence that the acidosis was not more severe during combined hypoxemia and hypercapnic acidosis than with [Sar1, Ala8]-AII. In addition, administration of the acetic acid vehicle with the vasopressin pressor antagonist during a normocapnic normocapnic time-control (n = 4) resulted in no evidence for systemic or renal vasodilation, acidosis, or other untoward effects.

It is doubtful that the splenectomy performed in the present study contributed to changes in renal function. Changes in hematocrit during acute hypoxemia or hypercapnic acidosis were minimal, compared with the increase in hematocrit from 39 to 47 with hypercapnic acidosis previously reported in unsplenectomized dogs (Borns et al., 1979). In addition, renal vasoconstriction has been previously observed during combined hypoxemia and hypercapnic acidosis in unsplenectomized conscious dogs (Koehler et al., 1980).

Taken together, the present investigation suggests that the renin-angiotensin system maintains renal hemodynamic function during combined hypoxemia and hypercapnic acidosis. However, the effects of the renin-angiotensin system on renal hemodynamic function during combined hypoxemia and hypercapnic acidosis can be evaluated definitively only by studies in which the angiotensin II inhibitor is infused selectively into the renal artery in doses that do not escape from the renal circulation with systemic effects.

In summary, neither acute hypoxemia nor acute hypercapnic acidosis alone results in renal dysfunction. In contrast, combined hypoxemia and hypercapnic acidosis acted synergistically to diminish renal hemodynamic function and urinary sodium excretion despite an increase in systemic arterial pressure. In view of the effects of angiotensin II inhibition, this study suggests that the renin-angi-
otensin system maintains renal hemodynamic function during combined hypoxemia and hypercapnic acidosis.

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INDEX TERMS: Acute hypoxemia • Acute hypercapnic acidosis • Acute respiratory failure • Renal dysfunction • Renin-angiotensin system • Angiotensin II • [Sar1, Ala3]-angiotensin II
Synergistic effects of acute hypoxemia and hypercapnic acidosis in conscious dogs. Renal
dysfunction and activation of the renin-angiotensin system.
C E Rose, Jr, D P Kimmel, R L Godine, Jr, D L Kaiser and R M Carey

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