Effect of α-Adrenergic Blockade on the Cardiovascular Responses to Hypoxemia and Hypercapnic Acidosis in Conscious Dogs (42843)

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Abstract. **In order to evaluate the role of the α-adrenergic system in the systemic and renal hemodynamic changes of the acute combined blood gas derangement, seven conscious mongrel dogs in careful sodium balance (80 mEq/day for 4 days) were evaluated. Each animal was evaluated during combined acute hypoxemia (PaO_2 = 35 ± 1 mm Hg) and hypercapnic acidosis ($PaCO_2$ = 56 ± 2 mm Hg; pH = 7.18 ± 0.01) with (i) vehicle (D5W) alone and (ii) α_1-adrenergic blockade with prazosin, 0.1 mg/kg iv. Mean arterial pressure increased during the combined blood gas derangement with vehicle. In contrast, mean arterial pressure fell during combined acute hypoxemia and hypercapnic acidosis with α_1-adrenergic blockade. The mechanism for abrogation of the rise in mean arterial pressure during the combined blood gas derangement by α_1-adrenergic blockade appeared to be through attenuation of the rise in cardiac output rather than an exaggerated fall in total peripheral resistance. These observations suggest that the α-adrenergic system is important in circulatory homeostasis during the combined blood gas derangement.** [P.S.E.B.M. 1989, Vol 190]

Cardiovascular performance is usually well maintained in human subjects and animals during mild to moderate degrees of acute hypoxemia (1–3), acute hypercapnic acidosis (2, 4), and combined acute hypoxemia and hypercapnic acidosis (2, 5). Preservation of cardiovascular performance during hypoxemia and hypercapnic acidosis is important in maintaining function of various organs under conditions of diminished arterial blood oxygen tension and pH. The importance of compensatory processes, such as increased blood pressure, in maintaining circulatory homeostasis is illustrated by observations in healthy human subjects by Schneider and Truesdell (3). Failure to increase blood pressure was associated with increased incidence of syncope. Although these observations suggest that a rise in systemic arterial pressure during hypoxemia or hypercapnic acidosis may be important, the mechanisms responsible for the systemic pressor response have not been elucidated clearly.

Previous observations in anesthetized, sympathectomized dogs suggest a major role for the sympathetic nervous system in maintenance of mean arterial pressure during acute hypoxemia (6) and hypercapnic acidosis (7). Important roles for angiotensin II and vasopressin in the increase in mean arterial pressure with combined acute hypoxemia and hypercapnic acidosis were recently identified using antagonists of these hormones in conscious dogs (8). However, two aspects of these recent observations suggest an important role for the sympathetic nervous system in systemic and renal cardiovascular function: (i) the initial rise of systemic arterial pressure in the first 10 min of the combined blood gas derangement was unaltered by simultaneous vasopressin and angiotensin II blockade; and (ii) major increases in circulating norepinephrine occurred during the combined blood gas derangement with simultaneous vasopressin pressor and angiotensin II blockade. Moreover, observations in conscious dogs revealed that parallel changes in circulating catecholamines and systemic arterial pressure occurred during combined hypoxemia and hypercapnic acidosis (9).

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The purpose of the present study was to evaluate the role of the α-adrenergic system in the rise in systemic blood pressure and renal hemodynamic function during combined hypoxemia and hypercapnic acidosis in conscious mongrel dogs.

Materials and Methods

Animal Preparation. Studies were performed on seven unanesthetized mongrel dogs weighing 16–26 kg. Preparatory surgery was performed prior to study and consisted of exteriorization of the left carotid artery into a "carotid loop," tracheostomy, and splenectomy. Splenectomy was performed to abolish the increase in hematocrit previously observed during acute hypercapnic acidosis in unsplenectomized dogs (10). All surgery was performed during pentobarbital anesthesia (30 mg/kg iv) under sterile conditions. Each animal was allowed at least 4 weeks for recovery from surgery before being studied in any protocols. Evidence for complete recovery from surgery included complete healing at incision sites, absence of fever, and normal food intake and exercise ability.

Sodium balance was established by daily administration of food containing less than 5 mEq of sodium (Hill's Prescription Diet h/d, Division of Riviana Foods, Topeka, KS) and intravenous infusion of 500 ml of 0.9% NaCl (75 mEq of sodium). This constant sodium intake of 80 mEq/24 hr was maintained for 4 days prior to study. Sodium balance was confirmed by a 24-hr urine collection just prior to study using a stainless steel metabolic cage.

On the morning of study, multiple catheters were inserted including an 18F urinary bladder catheter (Travenol Laboratories, Inc., Deerfield, IL), 18-gauge carotid loop catheter (Becton-Dickinson, Rutherford, NJ), and central venous catheter (PE 160; Clay Adams Division, Becton-Dickinson, Parsippany, NJ) via the right external jugular vein. The vascular catheters described above were inserted percutaneously following skin preparation with an iodine solution and intradermal lidocaine anesthesia. This was followed by insertion of a tracheostomy tube (9.7 mm internal diameter; Portex, Inc., Wilmington, MA) with inflation of the cuff to adequate seal.

The animal was then positioned for the study in a Pavlovian sling. Following iodine preparation of the skin, an 18-gauge catheter (Critikon, Tampa, FL) was inserted into a foreleg vein. An infusion of 5% dextrose in water (D5W) was administered that contained concentrations of inulin and *p*-aminohippurate sufficient to establish blood levels of 15–20 mg/dl and 1–3 mg/dl, respectively. The tracheostomy tube was attached to a mixing chamber using corrugated plastic tubing and a Rudolph valve such that inspired gas passed through the mixing chamber into the animal and expired gas passed out into the room.

Protocols. After waiting at least 1 hr for the animal to stabilize, the protocols were begun. Control measurements were obtained during 2 consecutive 20-min periods (0–40 min). In the subsequent 5-min intermediate period (40–45 min), a bolus injection of prazosin or its vehicle alone (D5W, 20 ml) was employed. Subsequently, two 20-min periods of combined hypoxemia and hypercapnic acidosis (45–85 min) were induced. Postcontrol measurements were obtained over two 20-min periods 40 min after cessation of the combined blood gas derangement (125–165 min). Each dog was studied in the following protocols on separate days at least 2 weeks apart:

Protocol I: combined acute hypoxemia and hypercapnic acidosis with vehicle alone ($n = 7$). This protocol was performed to assess the effects of combined acute hypoxemia and hypercapnic acidosis in adrenergically intact animals. Following control measurements, the prazosin vehicle (D5W, 20 ml) was administered as a bolus injection in the intermediate period. In addition, the vehicle (D5W) was infused at 0.5 ml/min during the intermediate period and both combined blood gas derangement periods (40–85 min).

Protocol II: combined acute hypoxemia and hypercapnic acidosis during α_1-adrenergic blockade ($n = 7$). To assess the role of the α_1-adrenergic component of the sympathetic nervous system, Protocol I was precisely repeated except that α_1-adrenergic blockade was induced just prior to the onset of combined hypoxemia and hypercapnic acidosis. Following completion of control measurements, prazosin hydrochloride (Pfizer, Inc., Groton, CT), 0.1 mg/kg in 20 ml of D5W, was injected slowly over 5 min in an intermediate period (40–45 min). Systolic arterial pressure, measured in six of the seven animals in the 5-min intermediate period, decreased ($P < 0.01$) from 148 ± 7 to 118 ± 6 mm Hg with prazosin administration. Following the injection of prazosin, the effects of combined hypoxemia and hypercapnic acidosis were then determined over two 20-min periods (45–85 min). The blood gas derangement was then stopped and after 40 min for recovery, postcontrol measurements were obtained over two 20-min periods (125–165 min).

To determine the degree of systemic α-adrenergic blockade, the systemic pressor response to intravenous phenylephrine (25 μg/kg) was determined immediately after completion of the blood gas derangement (85 min). Intact α-adrenergic responses to comparable injections of phenylephrine at the completion of the combined blood gas derangement were obtained in five of the seven animals in another protocol in the presence of β-adrenergic blockade with propranolol. The time sequence of the protocol and severity and duration of the combined blood gas derangement were identical to the present protocols. The β-adrenergic blockade studies have been previously reported (8). Injection of phen-

ylephrine following prazosin administration in Protocol II resulted in a rise (Δ) in mean arterial pressure of 5 ± 2 mm Hg ($n = 7$) which was significantly attenuated ($P < 0.005$) compared with a rise of 35 ± 6 mm Hg when phenylephrine was administered during intact α-adrenergic function ($n = 5$). It is possible that β-adrenergic blockade may have modified the systemic arterial pressure response to phenylephrine. However, Fujii and Vatner (11) observed that administration of a smaller intravenous dose of phenylephrine (2 μg/kg) to intact conscious dogs in the absence of β-adrenergic blockade resulted in a rise in arterial pressure of 40 mm Hg. These observations coupled with the systemic pressor response to phenylephrine during β-adrenergic blockade underscore the effectiveness of α-adrenergic blockade in the present study with major attenuation of the rise in mean arterial pressure to phenylephrine.

Protocol III: prazosin administration during normoxemia and normocapnia ($n = 7$). The systemic hemodynamic effects of prazosin are well known (12). To control for these effects, Protocol II was precisely repeated in the same seven dogs, except the animals breathed room air throughout the protocol. Prazosin hydrochloride (0.1 mg/kg) was administered intravenously over 5 min (40–45 min) following completion of control measurements. Measurements were then taken over two 20-min treatment periods (45–85 min). Administration of intravenous phenylephrine (25 μg/kg) at the end of these treatment periods (85 min) resulted in a rise in mean arterial pressure of 3 ± 3 mm Hg ($n = 7$), which was significantly reduced ($P < 0.005$) from 35 ± 6 mm Hg ($n = 5$) with a comparable dose of phenylephrine during intact α-adrenergic function on an alternate day. After 40 min had elapsed, postcontrol measurements were obtained over two 20-min periods (125–165 min).

Induction of Combined Blood Gas Derangement. Combined acute hypoxemia and hypercapnic acidosis were induced by adding 100% N_2 and 100% CO_2 to the inspired air via the mixing chamber, until the end tidal oxygen fraction (F_EO_2), measured by a fuel cell oxygen analyzer (Applied Technical Products, Denver, CO), decreased to 0.07, and the end tidal carbon dioxide fraction (F_ECO_2), measured by an infrared CO_2 analyzer (LB-2; Beckman Instruments, Fullerton, CA), increased to 0.085. Minute ventilation was calculated by performing a timed collection of expired gas with determination of volume on a 9-liter respirometer (Warren E. Collins, Braintree, MA).

Tolerance of Blood Gas Derangement by the Animals. Because the cardiovascular and renal effects of barbiturate anesthesia (13) and positive pressure ventilation (14) would cloud the cardiovascular effects of hypoxemia and hypercapnic acidosis, the animals were studied while conscious and spontaneously breathing. Before being conducted, the protocols were approved by the responsible veterinarian at the University of Virginia, who judged that they conformed to the principles outlined in the *Guide for the Care and Use of Laboratory Animals* (NIH Publication No. 85-23) by the National Institutes of Health. The facilities for laboratory animal research at the University of Virginia have been accredited by the American Association for Accreditation of Laboratory Animal Care since February 11, 1980. Measures employed as safeguards to limit stress to the animal included gradual induction of the blood gas derangement, limitation of the severity of hypercapnia to $PaCO_2 < 60$ mm Hg, and constant reassurance and petting by an investigator familiar to the animal during the hypoxemia and hypercapnia. Moreover, the investigator constantly monitored the animal's status, and the blood gas derangement was promptly discontinued if the animal exhibited signs of excessive stress or cardiovascular instability. Following the combined blood gas derangement, the animals exhibited signs of excellent condition, including return of cardiovascular indices to baseline, a voracious appetite, and exercise ability.

Hemodynamic Measurements and Assays. Systemic arterial and central venous pressures were measured from the carotid loop and external jugular catheters, respectively, using vascular transducers (P23Db; Gould-Statham, Hato Rey, PR) zeroed 5 cm dorsal to the sternum in the upright animal. Cardiac output was measured in duplicate each 20-min period according to the Stewart-Hamilton method (15) by central venous injection of indocyanine green dye with arterial blood analysis by withdrawing arterial blood through a cuvette densitometer (Gilford Instrument Laboratories, Inc., Oberlin, OH) using a withdrawal pump (Harvard Apparatus Co., South Natick, MA). Systemic arterial and central venous pressures were measured at 2, 4, 6, 14, 16, and 18 min into each 20-min period. These hemodynamic pressure measurements bracketed the multiple measurements of cardiac output, obtained at the midpoint (between 6 and 14 min) of each 20-min period. Chronologic changes within each 20-min period were determined by calculating separate means for pressure measurements at 2, 4, and 6 min and at 14, 16, and 18 min. Total peripheral resistance was calculated by dividing mean arterial pressure by cardiac output. Resistance units were converted from mm Hg/ml/sec to dynes sec cm^{-5} by multiplying by 1332.

Blood was obtained at the midpoint of each 20-min urine collection period. Plasma and urine inulin and *p*-aminohippurate concentrations were measured by spectrophotometry according to the methods of Heyrovsky (16) and Brun (17), respectively. Since indocyanine green dye was used to measure cardiac output, an analysis of the effects of the dye on spectrophotometric measurement of *p*-aminohippurate and inulin was performed. The addition of indocyanine green dye

in excess of maximal blood concentrations of 24 mg/liter to distilled water containing incremental amounts of inulin (20–100 mg/dl) or *p*-aminohippurate (0.5–5.0 mg/dl) used as standards for the assay failed to change the absorbance by spectrophotometry compared with determinations on identical standards which did not contain the dye. A high degree of correlation in spectrophotometric absorbance between the standards with and without indocyanine green dye was observed for inulin (slope 0.9, $r = 0.995$, $P < 0.001$) and *p*-aminohippurate (slope 1.1, $r = 0.999$, $P < 0.001$).

Specimens for plasma renin activity were collected in prechilled tubes containing EDTA, centrifuged at 4°C, and the plasma was stored at −80°C until the radioimmunoassay (18) was performed. Arterial blood gases were analyzed by appropriate electrodes (Model 113; Instrumentation Laboratory, Inc., Lexington, MA).

Data Analysis. Data were analyzed by one- and two-way analysis of variance with Student-Newman-Keuls multiple comparisons test (19). Unless stated, all comparisons can be considered statistically insignificant at $P \geq 0.05$. Throughout the text, tables, and figures, all data are expressed as the mean ± SE.

Results

Alterations in Arterial Blood Gases and Plasma Renin Activity during Combined Hypoxemia and Hypercapnic Acidosis. The severities of hypoxemia, hypercapnic acidosis, and hyperpnea were comparable among protocols (Table I). Plasma renin activity increased comparably during combined hypoxemia and hypercapnic acidosis with vehicle alone and α_1-adrenergic blockade in Protocols I and II (Table I).

Systemic Hemodynamic Effects of Combined Hypoxemia and Hypercapnic Acidosis during α_1-Adrenergic Inhibition. Mean arterial pressures during the control periods were comparable for all protocols (Fig. 1). Chronologic analysis of the change in mean arterial pressure during combined hypoxemia and hypercapnic acidosis with vehicle in Protocol I revealed an early sharp rise in mean arterial pressure in the initial 10 min of the combined blood gas derangement which was sustained over the subsequent 30 min (Fig. 1). In contrast, α_1-adrenergic blockade abrogated the early sharp rise in mean arterial pressure during the combined blood gas derangement, and mean arterial pressure fell progressively with continuation of combined hypoxemia and hypercapnic acidosis.

Total peripheral resistance decreased comparably during combined hypoxemia and hypercapnic acidosis with vehicle alone and α_1-adrenergic blockade (Fig. 2). In contrast to the comparable decrease in total peripheral resistance during the combined blood gas derangement with vehicle vs prazosin, administration of prazosin attenuated the rise in cardiac output during combined hypoxemia and hypercapnic acidosis (Fig. 3). Total peripheral resistance was comparable during the

Table I. Changes in Arterial Blood Gases with Combined Acute Hypoxemia and Hypercapnic Acidosis during α-Adrenergic Blockade

Protocols	Control (0–40 min)	Combined hypoxemia and hypercapnia or normal gas exchange (45–85 min)	Postcontrol (125–165 min)
Combined Blood Gas Derangement with			
I. Vehicle alone ($n = 7$)			
PaO_2[a] (mm Hg)	84 ± 2	33 ± 1*	82 ± 4
$PaCO_2$ (mm Hg)	34 ± 2	58 ± 2*	33 ± 2
pH	7.35 ± 0.01	7.17 ± 0.02*	7.37 ± 0.01
V_E (liter $min^{-1}kg^{-1}$)	0.20 ± 0.04	2.56 ± 0.14*	0.19 ± 0.03
PRA (ng ang I/ml/hr)	1.5 ± 0.6	7.4 ± 2.2*	2.4 ± 0.6
II. α-Adrenergic blockade ($n = 7$)			
PaO_2 (mm Hg)	84 ± 2	35 ± 1*	85 ± 2
$PaCO_2$ (mm Hg)	31 ± 2	55 ± 1*	30 ± 2
pH	7.38 ± 0.01	7.18 ± 0.01*	7.39 ± 0.01
V_E (liter $min^{-1}kg^{-1}$)	0.19 ± 0.03	2.33 ± 0.24*	0.18 ± 0.03
PRA (ng ang I/ml/hr)	0.8 ± 0.2	4.9 ± 1.6*	2.9 ± 1.0
Normal gas exchange with			
III. α_1-Adrenergic blockade ($n = 7$)			
PaO_2 (mm Hg)	78 ± 3	82 ± 2	84 ± 2*
$PaCO_2$ (mm Hg)	29 ± 1	29 ± 2	30 ± 2
pH	7.39 ± 0.02	7.40 ± 0.01	7.42 ± 0.01*
V_E (liter $min^{-1}kg^{-1}$)	0.15 ± 0.03	0.15 ± 0.02	0.15 ± 0.01
PRA (ng ang I/ml/hr)	0.8 ± 0.2	1.3 ± 0.2*	1.6 ± 0.3*

[a] PaO_2, arterial blood oxygen tension; $PaCO_2$, arterial blood carbon dioxide tension; pH, arterial blood pH; V_E, minute ventilation; PRA, plasma renin activity.
*Denotes significant difference from protocol control value, $P < 0.05$.

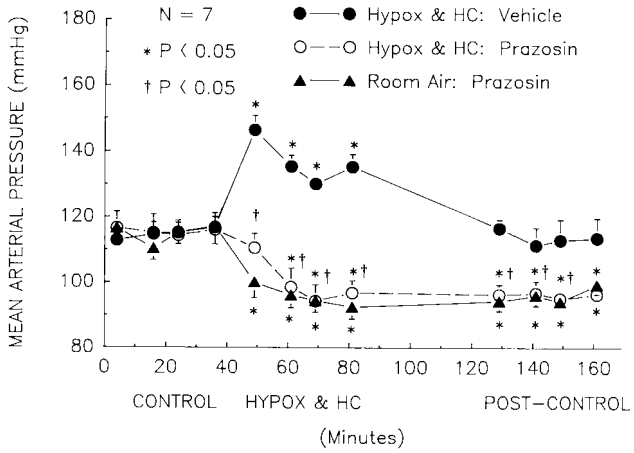

Figure 1. In contrast to the early and sustained rise in mean arterial pressure during the combined blood gas derangement with vehicle (●——●), mean arterial pressure fell progressively during combined acute hypoxemia and hypercapnic acidosis with α_1-adrenergic inhibition (O– – –O). Mean arterial pressure also fell with prazosin administration during normal gas exchange (▲——▲). * Denotes statistically significant difference from respective protocol control period. † Denotes statistically significant difference between combined blood gas derangement with vehicle alone compared with combined acute hypoxemia and hypercapnic acidosis with α_1-adrenergic blockade.

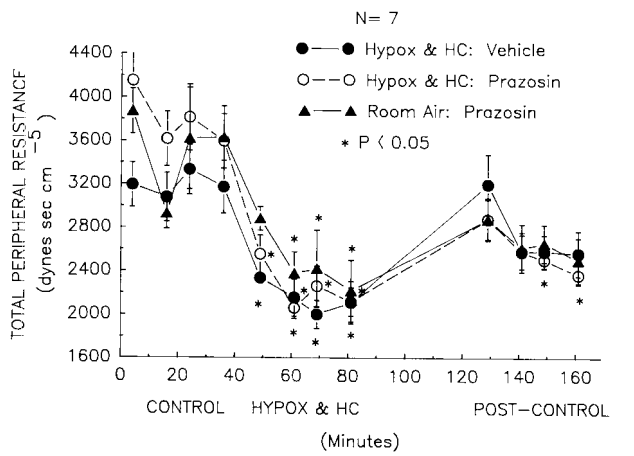

Figure 2. Total peripheral resistance fell comparably during the combined blood gas derangement with vehicle (●– – –●), the combined blood gas derangement with prazosin (O– – –O), and normal gas exchange with prazosin (▲——▲). * Denotes statistically significant difference from respective protocol control period.

control periods between protocols. Although cardiac output was slightly lower during the initial 20-min control period, cardiac outputs were comparable among all protocols in the second 20-min control period just prior to the combined blood gas derangement.

Stroke volume was unchanged from control to the combined blood gas derangement with vehicle and α_1-adrenergic blockade (Table II). However, stroke volume fell in the initial postcontrol period following the combined blood gas derangement with prazosin. Central venous pressure remained unchanged from control during combined hypoxemia and hypercapnic acidosis with vehicle alone and α_1-adrenergic blockade (Table

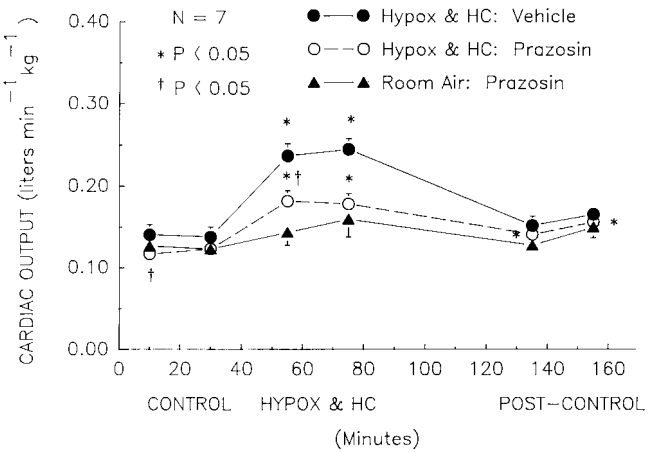

Figure 3. The rise in cardiac output during the combined blood gas derangement with vehicle (●——●) was attenuated by α_1-adrenergic blockade (O– – –O). Cardiac output was unchanged by α_1-adrenergic blockade during normal gas exchange (▲——▲). * Denotes statistically significant difference from respective protocol control period. † Denotes statistically significant difference between the combined blood gas derangement with vehicle alone compared with combined acute hypoxemia and hypercapnic acidosis with α_1-adrenergic blockade.

II). Heart rate increased comparably during combined acute hypoxemia and hypercapnic acidosis with vehicle alone and during α-adrenergic blockade (Table II). However, heart rate remained elevated in the postcontrol periods following the combined blood gas derangement with prazosin, in contrast to the other protocols. Central venous pressure and heart rate were comparable in control periods among protocols. Stroke volume was slightly decreased in the initial 20-min control period of the combined blood gas derangement with α_1-adrenergic blockade, but was comparable among protocols in the second 20-min control period.

Renal Hemodynamic Effects of Combined Hypoxemia and Hypercapnic Acidosis during α_1-Adrenergic Blockade. Control measurements for glomerular filtration rate and effective renal plasma flow were comparable among the protocols. Glomerular filtration rate decreased during the first 20 min of combined acute hypoxemia and hypercapnic acidosis in the presence of vehicle alone or with α_1-adrenergic blockade, but returned toward baseline in the second 20 min of the combined blood gas derangement (Table III). Effective renal plasma flow similarly fell during the first 20 min of combined acute hypoxemia and hypercapnic acidosis with vehicle alone and α_1-adrenergic blockade but was unchanged in the second 20-min period (Table III).

Effects of Prazosin Administration Alone. Although the animals breathed room air during the entire protocol, PaO_2 and pH increased ($P < 0.05$) slightly in the postcontrol period following prazosin administration. Plasma renin activity increased slightly with prazosin administration and in the postcontrol period (Table I).

Table II. Systemic Hemodynamic Function with Combined Acute Hypoxemia and Hypercapnia Acidosis during α-Adrenergic Blockade

Protocols	Control		Combined hypoxemia and hypercapnia or normal gas exchange		Postcontrol	
	0–20 min	20–40 min	45–65 min	65–85 min	125–145 min	145–165 min
Combined blood gas derangement with						
I. Vehicle alone ($n = 7$)						
SV (ml $min^{-1}kg^{-1}$)	1.8 ± 0.2	1.8 ± 0.2	2.0 ± 0.2	2.1 ± 0.1	1.8 ± 0.1	1.9 ± 0.1
CVP (mm Hg)	1 ± 1	1 ± 1	3 ± 2	1 ± 1	0 ± 1	0 ± 1
HR (beats/min)	78 ± 6	78 ± 6	119 ± 7*	120 ± 7*	85 ± 6	88 ± 7
II. α-Adrenergic blockade ($n = 7$)						
SV (ml $min^{-1}kg^{-1}$)	1.5 ± 0.1†	1.6 ± 0.2	1.7 ± 0.1	1.6 ± 0.2	1.2 ± 0.1*†	1.5 ± 0.3
CVP (mm Hg)	3 ± 1	2 ± 1	1 ± 1	1 ± 2	1 ± 1	0 ± 1
HR (beats/min)	84 ± 10	84 ± 9	115 ± 8*	116 ± 9*	117 ± 1.2*	113 ± 15*
Normal gas exchange with						
III. α_1-Adrenergic blockade ($n = 7$)						
SV (ml $min^{-1}kg^{-1}$)	1.9 ± 0.2	1.7 ± 0.2	1.5 ± 0.2	1.7 ± 0.2	1.5 ± 0.2	1.9 ± 0.4
CVP (mm Hg)	1 ± 1	1 ± 1	1 ± 1	1 ± 1	1 ± 1	0 ± 1
HR (beats/min)	70 ± 6	77 ± 8	98 ± 8*	98 ± 13*	92 ± 8	86 ± 10

[a] SV, stroke volume; CVP, central venous pressure; HR, heart rate.
* Denotes significant difference from protocol control values, $P < 0.05$. † Denotes statistically significant difference between the combined blood gas derangement with α_1-adrenergic blockade versus vehicle, $P < 0.05$.

Table III. Renal Hemodynamic Changes with Combined Hypoxemia and Hypercapnic Acidosis during α-Adrenergic Blockade

Protocols	Control		Combined hypoxemia and hypercapnia or normal gas exchange		Postcontrol	
	0–20 min	20–40 min	45–65 min	65–85 min	125–145 min	145–165 min
Combined blood gas derangement with						
I. Vehicle alone ($n = 7$)						
GFR[a] (ml $min^{-1}kg^{-1}$)	2.0 ± 0.3	2.4 ± 0.4	0.9 ± 0.1*	1.5 ± 0.4	2.7 ± 0.3	2.5 ± 0.4
ERPF (ml $min^{-1}kg^{-1}$)	7.7 ± 1.1	9.7 ± 1.6	3.5 ± 0.6*	6.2 ± 1.5	9.1 ± 1.1	9.7 ± 0.9
II. α_1-Adrenergic blockade ($n = 7$)						
GFR (ml $min^{-1}kg^{-1}$)	2.7 ± 0.3	3.0 ± 0.3	1.0 ± 0.4*	2.4 ± 0.4	2.9 ± 0.3	2.9 ± 0.3
ERPF (ml $min^{-1}kg^{-1}$)	11.7 ± 2.1	12.3 ± 2.1	3.8 ± 1.4*	10.6 ± 2.6	11.0 ± 1.7	11.6 ± 1.4
Normal gas exchange with						
III. α_1-Adrenergic blockade ($n = 7$)						
GFR (ml $min^{-1}kg^{-1}$)	2.2 ± 0.2	2.5 ± 0.2	1.8 ± 0.3	2.7 ± 0.3	2.9 ± 0.3	3.4 ± 0.4
ERPF (ml min^{-1} kg^{-1})	7.9 ± 1.2	9.8 ± 0.9	6.8 ± 0.7	15.6 ± 4.3	10.8 ± 1.2	12.4 ± 1.1

[a] GFR, glomerular filtration rate; ERPF, effective renal plasma flow.
* Denotes significant difference from protocol control value, $P < 0.05$.

Prazosin administration resulted in a fall in mean arterial pressure, which remained decreased ($P < 0.05$) in the postcontrol period (Fig. 1). The decrease in mean arterial pressure from control with prazosin administration was comparable to the decrease in mean arterial pressure from control to combined hypoxemia and hypercapnic acidosis with α_1-adrenergic blockade in Protocol II (Fig. 1). Although unchanged in the first 10 min following administration, total peripheral resistance decreased throughout the rest of the protocol including the postcontrol measurements (Fig. 2). Central venous pressure, stroke volume (Table II), and cardiac output (Fig. 3) were unchanged, but heart rate increased following prazosin administration (Table II). Glomerular filtration rate and effective renal plasma flow were unchanged following prazosin administration (Table III).

Discussion

The present study was performed to evaluate the role of α adrenoceptors in the systemic circulatory and renal hemodynamic changes during combined acute hypoxemia and hypercapnic acidosis. This study suggests that α_1-adrenoceptors contribute to the rise in mean arterial pressure during the combined blood gas derangement, including the early rise in the first 10 min

in mean arterial pressure with combined acute hypoxemia and hypercapnic acidosis.

Mean arterial pressure rose during the combined blood gas derangement with vehicle because the increase in cardiac output exceeded the fall in total peripheral resistance. The mechanism of obliteration of the systemic pressor response by α_1-adrenergic blockade during combined hypoxemia and hypercapnic acidosis appears to be through attenuation of the rise in cardiac output rather than a greater fall in total peripheral resistance as compared with the combined blood gas derangement with vehicle alone. This contrasts with the fall in arterial pressure with prazosin administration during normal gas exchange, which was associated with diminished systemic arterial resistance rather than any change in cardiac output. The role of the β-adrenergic system during combined acute hypoxemia and hypercapnic acidosis has been recently evaluated in conscious dogs (8). Institution of β-adrenergic blockade with propranolol during combined hypoxemia and hypercapnic acidosis in conscious dogs abolished the fall in total peripheral resistance and attenuated but did not abolish the rise in cardiac output with resulting increase in mean arterial pressure (8). Thus, the β-adrenergic system appears to predominantly mediate the decrease in total peripheral resistance, but only partially contributes to the rise in cardiac output during the combined blood gas derangement. Simultaneous vasopressin pressor and angiotensin II blockade during the combined blood gas derangement failed to alter the rise in cardiac output, but led to an exaggerated fall in total peripheral resistance with abolition of the rise in systemic arterial pressure (8). Taken altogether, these findings suggest that the role of α and β adrenoceptors, vasopressin and angiotensin II in the systemic pressor response during combined hypoxemia and hypercapnic acidosis depends on their influence of the balance between the increase in cardiac output vs decrease in total peripheral resistance.

The attenuation of the rise in cardiac output during the combined blood gas derangement by α_1-adrenergic blockade suggests that the α-adrenergic system contributes to increased cardiac output during combined acute hypoxemia and hypercapnic acidosis. Three possible explanations may be presented to explain the attenuation in the rise in cardiac output with prazosin during the combined acute blood gas derangement: (i) prazosin exerts central effects to diminish sympathetic neural discharge (20); (ii) α-adrenergic blockade diminishes venous tone, increases venous capacitance, and decreases venous return to the heart (21); and (iii) α-adrenergic blockade inhibits a positive inotropic effect of cardiac α adrenoceptors (22). A central action of prazosin to decrease sympathetic neural discharge can be supported by observations that intravenous prazosin (0.05 mg/kg) significantly reduced pre- and postganglionic sympathetic neural discharge in baroreceptor denervated cats (20). However, the overwhelming evidence points to a peripheral and not central action of prazosin on arterial pressure (21). Comparable central venous pressure during the combined blood gas derangement with prazosin vs vehicle is against the possibility that prazosin attenuated cardiac output through decreased blood return to the heart secondary to increased venous capacitance. With regard to the last possibility, a growing body of evidence supports the existence of a positive inotropic effect of α adrenoceptor stimulation in mammalian cardiac tissue (22). Gengo *et al.* (22) very recently reported increased contractility of rat right ventricular muscle strips with phenylephrine in the presence of β-adrenergic blockade. Administration of the selective α-adrenergic agonist methoxamine to anesthetized, mechanically ventilated, heart rate-controlled Dorset lambs resulted in an increase in the left ventricular contractility index dP/dt (23). This effect of methoxamine on contractility was abolished by phentolamine. In further support of a positive inotropic effect of α adrenoceptors, α-adrenergic blockade by itself has been found to decrease cardiac contractility. α-Adrenergic blockade with intravenous prazosin (0.49 mg/kg) in conscious dogs at constant heart rate resulted in diminished left ventricular dP/dt (24). Although we have no direct information, these previous observations suggest that prazosin may have attenuated the rise in cardiac output during hypoxemia and hypercapnic acidosis by blocking a positive inotropic action of cardiac adrenoceptors.

Previous studies which have evaluated the role of the α-adrenergic system during acute blood gas derangements have been limited to fetal (25) or anesthetized animals (26) and to acute hypoxemia (25) or acute hypercapnic acidosis (26) alone. To our knowledge, the present study is the first to evaluate the effects of α-adrenergic blockade during combined hypoxemia and hypercapnic acidosis in conscious adult animals in the absence of the clouding effects of barbiturate anesthesia (13).

The decrease in mean arterial pressure with prazosin administration during normal gas exchange is comparable to previous observations in indomethacin-treated, anesthetized dogs (12). Increase in heart rate with prazosin alone in the present study has been observed in previous investigations. Heart rate increased with intravenous prazosin administration of 0.49 mg/kg to conscious dogs (24) and intravenous injection of prazosin (0.2 mg/kg) in indomethacin-treated, anesthetized dogs (12).

The reason for variation in cardiac output and stroke volume in the control periods is unclear, since each animal was used as its own control by being studied in all protocols. We have previously observed between study variation in cardiac output when the

same group of dogs were studied in multiple protocols (2, 8).

The present observations provide no insight into the role of α adrenoceptors or other mechanisms in the diminished renal hemodynamic function during combined acute hypoxemia and hypercapnic acidosis. Failure of prazosin to alter the fall in renal hemodynamic function during acute hypoxemia and hypercapnic acidosis does not exclude a role for α adrenoceptors since abolition of the rise in mean arterial pressure and renal perfusion pressure by prazosin may have offset the effect of blockade of renal α adrenoceptors. To clearly elucidate the role of α adrenoceptors in the renal vasoconstriction with the combined blood gas derangement, future studies should be performed where α-adrenergic blockade is confined to the kidney.

α_1-Adrenergic blockade with prazosin abolished the systemic pressor response but not the renal vasoconstriction with combined acute hypoxemia and hypercapnic acidosis in conscious dogs. These findings suggest that the α-adrenergic system is important in the maintenance of circulatory homeostasis during combined acute hypoxemia and hypercapnic acidosis.

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