Right Ventricular Performance during Increased Afterload Impaired by Hypercapnic Acidosis in Conscious Dogs

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SUMMARY. Since heart failure may occur in the setting of lung dysfunction and CO2 retention with only modest increases in cardiac work load, we questioned whether myocardial function is impaired by hypercapnic acidosis. To determine the influence of hypercapnic acidosis on right ventricular function, we measured the effects of acute (2 hours) and chronic (2 weeks) hypercapnic acidosis on right ventricular performance during normal and increased right ventricular afterload in five conscious dogs. Systemic hemodynamic and right ventricular functions were unaltered during normal right ventricular afterload by acute hypercapnic acidosis (Paco2 = 49 ± 3 mm Hg, pH = 7.27 ± 0.003). As right ventricular afterload was increased by progressive balloon occlusion of the right ventricular outflow tract during acute hypercapnic acidosis, the rise (slope) in right ventricular end-diastolic pressure was increased 4-fold (P < 0.01) over that observed in normocapnic control. Maximum isovolumic right ventricular dP/dt rose (P < 0.05) comparably with increasing right ventricular afterload during normocapnic control and acute hypercapnic acidosis. Chronic hypercapnic acidosis (Paco2 = 55 ± 2 mm Hg, pH = 7.28 ± 0.01) resulted in systemic vasodilation and increased (P < 0.05) heart rate and cardiac output during normal right ventricular afterload. As right ventricular afterload was increased during chronic hypercapnic acidosis, the rate of rise in right ventricular end-diastolic pressure was 2-fold (P < 0.01) above normocapnic control but maximum isovolumic right ventricular dP/dt was unchanged in contrast to normocapnic control and acute hypercapnic acidosis. Moreover, cardiac output fell and stroke work was unchanged with increasing afterload during chronic hypercapnic acidosis. We conclude that hypercapnic acidosis results in diminished right ventricular performance during increased right ventricular afterload, evidenced by accentuated rise in right ventricular end-diastolic pressure, and may contribute to the congestive heart failure and edema observed in patients with pulmonary hypertension and CO2 retention. (Circ Res 52: 76–84, 1983)

ALTHOUGH right ventricular (RV) failure and edema occur frequently in patients with severe pulmonary dysfunction (Ferrer and Harvey, 1959), their pathogenesis remains unclear. Pulmonary hypertension with excessive RV work has been cited as the major causative factor (Oakley and Goodwin, 1967; Ferrer, 1975), and clinical studies have documented higher pulmonary arterial pressures in patients with chronic obstructive lung disease complicated by heart failure (Harvey et al. 1951; Whitaker, 1954; Aber et al., 1963). However, in conditions such as high altitude pulmonary hypertension (Penloza et al., 1970) and Tetralogy of Fallot (Kirklin and Karp, 1970), exceedingly high RV workloads great enough to limit cardiac output and cause syncpe are rarely associated with heart failure. In contrast, patients with chronic obstructive lung disease, especially of the “blue bloater” type (Burrows et al., 1966), frequently develop congestive heart failure, often with only moderate increases in RV workload (Aber et al., 1963). Since hypoxemia and hypercapnic acidosis are consistent features of the “blue bloater” variety of chronic obstructive lung disease (Burrows et al., 1966; Burrows and Earle, 1969), it is possible that these blood gas derangements have a pathogenic role in the development of heart failure in the presence of increased RV afterload, independent of their role in increasing RV afterload.

The uncommon occurrence of congestive heart failure in patients with marked hypoxemia associated with Tetralogy of Fallot suggests hypoxemia has little, if any importance in the pathogenesis of heart failure. On the other hand, hypercapnic acidosis is commonly associated with edema and heart failure in patients with chronic obstructive lung disease (Platts and Greaves, 1957), and the onset of CO2 retention has been suggested as a useful predictor of the subsequent development of edema (Platts and Greaves, 1957; Campbell and Short, 1960).

All of this suggests that hypercapnic acidosis may impair RV performance, especially in the presence of...
increased RV afterload. Since the hallmark of RV failure in patients with lung disease is elevated RV end-diastolic pressure, the objective of the present study was to determine whether hypercapnic acidosis would impair the ability of the RV to maintain a low end-diastolic pressure in the face of increased afterload. Therefore, the present study measured RV performance during acute and chronic hypercapnic acidosis with normal and increased RV afterload.

**Methods**

**Preparation of Animals**

Mongrel dogs weighing from 24.5 to 30.6 kg underwent preparatory surgery after having been screened for heartworm infection. The surgery was done in three stages under pentobarbital anesthesia (30 mg/kg, iv) and consisted of (1) exteriorization of the left carotid artery into a “carotid loop” (Child and Glen, 1938) and splenectomy, (2) tracheostomy, and (3) right thoracotomy. The carotid loop was constructed to allow convenient and repeated access to the arterial circulation by percutaneous catheterization on the day of the study. Splenectomy was performed to minimize hematocrit and blood volume variation during hypercapnia. The thoracotomy was done in order to implant pacing wires on the right atrial appendage. The pacing wires were exited through a stab wound in the right posterior scapular area. Because of evidence that indices of right ventricular contractility vary with change in heart rate (Vatner and Braunwald, 1974), we chose to employ atrial pacing (Medtronic Atrial Pacemaker 5320) at a pacemaker rate of 140/min during control and hypercapnic conditions.

At least 2 weeks were allowed for recovery from these surgical procedures. During this time, complete healing of all surgical sites occurred, and all animals exhibited normal food intake and exercise ability.

Vascular and pleural catheters were inserted on the day of the study using local anesthesia with lidocaine hydrochloride. A percutaneous 20-gauge catheter was inserted into the carotid loop for measurement of systemic arterial pressure and sampling of arterial blood. Under fluoroscopic guidance, a 5F micromanometer tip catheter (PC460, Millar Instruments) was inserted into the RV via a sterile cut-down through the external jugular vein. In addition, a 2F triple-lumen balloon occlusion catheter (Laks Catheter, Edwards Laboratories) was inserted so that the proximal port was positioned in the RV, the distal port was in the pulmonary artery, and the balloon was in the pulmonary artery outflow tract. Progressive balloon inflation resulted in an increase in afterload to the right ventricle. A 5F Swan Ganz catheter (Edwards Laboratories) was inserted through the external jugular vein by fluoroscopic guidance to a permanent wedge position in the pulmonary artery for measurement of pulmonary arterial wedge pressure. After insertion of the vascular catheters, a catheter (PE 240, Clay Adams) was inserted percutaneously into the left pleural space with an 11-gauge needle introducer.

A tracheostomy tube was inserted and connected through a two-way Rudolph valve by corrugated tubing to a 2-liter plastic mixing chamber such that ambient room air passed through the mixing chamber to the animal during inhalation. Exhaled gas exited through the Rudolph valve into the room.

After preparation, each animal was positioned to stand comfortably in a Pavlovian sling (Alice King Chatham) for the protocol.

**Hemodynamic Measurements**

Systemic arterial, pulmonary arterial, and pleural pressures were measured with conventional transducers (P23Db, Statham Instruments, Inc) zeroed to the upright animal's mid-chest. Right ventricular pressure was measured with the micromanometer tip catheter, and transmural right ventricular pressure was obtained by an electrical circuit that subtracted intrapleural pressure from right ventricular pressure. We found the subtraction system to be free of significant distortion or phase shift to 16 Hz using a pressure generator (MPG-30, Millar Instruments). Transmural RV end-diastolic pressure (RVEDP) was calculated manually from a strip chart recording by averaging values over 8–10 cardiac cycles.

Right ventricular function was estimated by an on-line digital computer (Nova 1200, Data General Corp.) which analyzed the transmural right ventricular pressure signal, using a program designed to calculate average systolic pressure and maximum dP/dt from at least 50 cardiac cycles. This system of measuring these indices of contractility has been validated in our laboratory for the left ventricle and described previously (Tucker et al., 1976). Measurement of dP/dt max was validated for the right ventricle using inotropic agents in a separate group of dogs. With isoproterenol infusion at 0.1 μg/kg per min, RV dP/dt max increased by 112% from 709 ± 55 to 1505 ± 122 mm Hg/sec. The β-receptor blocker, metoprolol (Lopressor, Ciba-Geigy) given in a dosage of 1 mg/kg resulted in a 26% decrease in RV dP/dt max from 830 ± 90 to 616 ± 76 mm Hg/sec. Since the accuracy of dP/dt max can be questioned if it occurs after opening of the pulmonic valve; we calculated the maximum isovolumic RV dP/dt (RV dP/dtIso) under varying afterload states during normocapnia and hypercapnic conditions. RV dP/dtIso was measured by determining dP/dt at pulmonary arterial end-diastolic pressure.

Cardiac output was measured by right ventricular injection of indocyanine green dye, with sampling of systemic arterial blood through a cuvette densitometer (D402A, Waters Instruments) and cardiac output was calculated by on-line computer analysis using the traditional Stewart-Hamilton technique (Hamilton et al., 1931). Total peripheral and pulmonary vascular resistances were calculated by dividing either mean systemic arterial or pulmonary arterial pressure (mm Hg) by cardiac output (ml/sec). Pulmonary arterial resistance was also calculated by subtracting the pulmonary arterial wedge pressure from mean pulmonary arterial pressure before dividing by cardiac output. Resistance values were corrected from mm Hg/ml per sec to dynes sec cm⁻⁵ by multiplying by 1332. Stroke volume was calculated by dividing the cardiac output by heart rate; stroke work was calculated by multiplying the stroke volume (ml) by the transmural right ventricular pulse pressure (peak systolic minus end-diastolic pressure, mm Hg). Stroke work was converted from ml mm Hg to gm M by multiplying by 0.0136.

Arterial blood gases were analyzed within 30 minutes of sampling with appropriate electrodes (Radiometer-Copenhagen) and were corrected to the animal’s body temperature. Minute ventilation was measured by timed collections of expired gas, after which the volume was measured in a spirometer (Warren E. Collins).

**Protocols**

**Acute Hypercapnic Acidosis**

Animals were studied on two separate days. On the first day, following measurements during normocapnia, after-
load was increased in four steps of approximately 8 mm Hg each. Variables were again measured at each stage of afterload. Total duration of afterload was approximately 30 minutes.

Ten minutes after removal of afterload, acute hypercapnic acidosis was induced by adding CO₂ to the inspired air (mixing chamber) until the end-tidal CO₂ fraction (Fₑ_CO₂), measured by an infrared CO₂ analyzer (LB-2 Beckman Instruments), was 0.085. The PaO₂ was kept in the physiological range during the ensuing hyperpnea by adding N₂ to the inspired air to maintain the end-tidal oxygen fraction (Fₑ_O₂), measured by a fuel cell oxygen analyzer (Applied Technical Products) at the control level. After 30 minutes of acute hypercapnic acidosis, measurements were obtained at existing RV afterload and following each increase in afterload.

Chronic Hypercapnic Acidosis

After completion of the acute hypercapnic acidosis protocol, animals were placed in a chronic hypercapnic environment. This was accomplished by employing an air-tight chamber in which CO₂ was added by a servo-system that maintained 8.5 ± 0.2% CO₂ in the chamber gas. All animals exhibited normal food intake and exercise ability during chronic hypercapnic acidosis, and weight was maintained.

After continuous exposure to CO₂ for 2 weeks, each animal was restudied. To maintain continuous exposure, CO₂ was administered via a tracheostomy tube during the actual study. The animal preparation, positioning, and atrial pacing were identical to the acute hypercapnic acidosis protocol.

Measurements were obtained at existing RV afterload and following step-wise increase in similar fashion to the acute study.

Role of the β-Adrenergic Nervous System

The effects of β-adrenergic stimulation were measured by infusion of isoproterenol hydrochloride from 0.005 to 0.1 µg/kg per min. This was done 10 minutes after the removal of afterload during normocapnia, acute, and chronic hypercapnic acidosis. After completion of the isoproterenol infusion, cardiac pacing was discontinued, at least 10 minutes elapsed, and the heart rate was allowed to return to normal before proceeding with the protocol.

Following the afterload trial during normocapnia and acute hypercapnic acidosis on the first day, and chronic hypercapnic acidosis on the second day, the effects of β₁-adrenergic blockade were assessed by administering metoprolol, 1 mg/kg, intravenously, followed by an infusion of 0.005 to 0.1 µg/kg per hr. The entire protocol then was repeated; this consisted of repeating measurements during normocapnia and acute hypercapnic acidosis on the first day and subsequently during chronic hypercapnic acidosis 2 weeks later.

The adequacy of the β-blockade was determined by isoproterenol infusion and measurement of RV contractility at the end of the protocol. With β₁-adrenergic blockade during acute hypercapnic acidosis, isoproterenol infusion of 0.1 µg/kg per min resulted in an increase of 11 ± 5% in dP/dt max, in contrast to 95 ± 26% increase without blockade. Using the same isoproterenol infusion rate, β₁-adrenergic blockade during chronic hypercapnic acidosis resulted in a 14 ± 8% increase in dP/dt max, in contrast to a 85 ± 26% increase, respectively, without blockade.

Statistical Analysis

Measurements at existing afterload during normocapnia, acute hypercapnic acidosis, and chronic hypercapnic acidosis were compared by two-way analysis of variance using Student-Newman-Keuls multiple comparison test (Steel and Torrie, 1960). Comparable periods before and after β-blockade were compared by one-way analysis of variance (Steel and Torrie, 1960). Statistical significance was inferred when P < 0.05.

The effects of afterload were examined using hypothesized models expressed as a linear equation with both class and interval independent variables (GLM procedure, Statistical Analysis System, SAS Institute, Inc.; version 79.3). This technique is similar to classical analysis of covariance, but with techniques which relax some of the limitations regarding balance within the design (Searle, 1971). The models were examined to compare pairs of effects by treatment (control, acute, and chronic hypercapnic acidosis, without and with metoprolol). Expression of each hemodynamic variable as a linear equation was based on (1) observation of a linear response in the raw data for all five animals, and (2) an acceptable r² value for expressing the data as a linear equation.

The results from the initial model were used to construct a final model (treatment alone, treatment and applied afterload, afterload alone, or treatment/afterload interaction) for which the relevant parameters (slopes and intercepts) then were estimated in order to construct the graphical representation of the experimental results as shown in Figure 2. Representative 95% confidence bands were plotted around the regression line using data from the five animals. Model terms were included in the final model if the partial F statistic in the initial model indicated a level of significance of 0.015 or less (making the overall criterion 0.05 or less when one considers two main effects and one interaction).

Results

Severity of Hypercapnic Acidosis (Table 1)

Arterial blood gas data were similar for studies performed prior to and following β-adrenergic blockade, and were pooled (Table 1). Serum bicarbonate concentration increased (P < 0.05) from control (normocapnia) of 20 ± 1 to 25 ± 1 mEq/liter during chronic hypercapnic acidosis providing evidence of renal compensation. However, arterial pH was similar (P = NS) during acute and chronic hypercapnic acidosis, probably due to increased Paco₂ during chronic hypercapnic acidosis. PaO₂ increased slightly (P <

<table>
<thead>
<tr>
<th></th>
<th>Control (normocapnia)</th>
<th>Acute hypercapnic acidosis</th>
<th>Chronic hypercapnic acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.38 ± 0.01</td>
<td>7.27 ± 0.003*</td>
<td>7.28 ± 0.01*</td>
</tr>
<tr>
<td>P CO₂ (mm Hg)</td>
<td>34 ± 2</td>
<td>49 ± 3*</td>
<td>55 ± 2*</td>
</tr>
<tr>
<td>P O₂ (mm Hg)</td>
<td>71 ± 2</td>
<td>70 ± 2</td>
<td>88 ± 2*</td>
</tr>
<tr>
<td>Minute ventilation (li-</td>
<td>4.3 ± 0.02</td>
<td>31.0 ± 3.6*</td>
<td>29.8 ± 2.2*</td>
</tr>
<tr>
<td>ters/min</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as means ± SEM.

* Significant difference from control, P < 0.05.
† Significant difference between acute and chronic hypercapnic acidosis, P < 0.05.
Table 2

Hemodynamic Effects of Hypercapnic Acidosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (normocapnia)</th>
<th>Acute hypercapnic acidosis</th>
<th>Chronic hypercapnic acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n = 5)</td>
<td>127 ± 8</td>
<td>137 ± 7</td>
<td>123 ± 6</td>
</tr>
<tr>
<td>β₁-Blockade (n = 4)</td>
<td>134 ± 9</td>
<td>145 ± 7</td>
<td>138 ± 8</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n = 5)</td>
<td>18 ± 1</td>
<td>21 ± 2</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>β₁-Blockade (n = 4)</td>
<td>19 ± 2</td>
<td>22 ± 2</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>Cardiac output (liters/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n = 5)</td>
<td>3.6 ± 0.2</td>
<td>4.1 ± 0.6</td>
<td>5.1 ± 0.2*</td>
</tr>
<tr>
<td>β₁-Blockade (n = 4)</td>
<td>3.7 ± 0.5</td>
<td>3.7 ± 0.4</td>
<td>4.6 ± 0.5</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n = 5)</td>
<td>31 ± 2</td>
<td>34 ± 2</td>
<td>38 ± 2</td>
</tr>
<tr>
<td>β₁-Blockade (n = 4)</td>
<td>35 ± 2</td>
<td>29 ± 3</td>
<td>34 ± 3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n = 5)</td>
<td>118 ± 3</td>
<td>118 ± 5</td>
<td>135 ± 3*</td>
</tr>
<tr>
<td>β₁-Blockade (n = 4)</td>
<td>118 ± 8</td>
<td>127 ± 5</td>
<td>134 ± 3*</td>
</tr>
<tr>
<td>Vascular resistance (dynes-sec-cm⁻³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total peripheral</td>
<td>2850 ± 267</td>
<td>2947 ± 512</td>
<td>1933 ± 114*</td>
</tr>
<tr>
<td>β₁-Blockade (n = 4)</td>
<td>2520 ± 102</td>
<td>3276 ± 414</td>
<td>2523 ± 388</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>397 ± 43</td>
<td>449 ± 71</td>
<td>266 ± 27</td>
</tr>
<tr>
<td>β₁-Blockade (n = 4)</td>
<td>365 ± 40</td>
<td>518 ± 97</td>
<td>328 ± 49</td>
</tr>
</tbody>
</table>

Values are expressed as means ± 1 SEM.  
* Significant difference from the control, P < 0.05.  
† Significant difference between acute and chronic hypercapnic acidosis, P < 0.05.

During acute hypercapnic acidosis, systemic hemodynamic variables (Table 2), right ventricular systolic and end-diastolic pressures, stroke work (Table 3), and RV dP/dt₅₀ (Table 4) were unchanged during acute hypercapnic acidosis. Both mean pulmonary wedge pressure and pulmonary arterial resistance were also unchanged (n = 4) during acute hypercapnic acidosis.

The RV hemodynamic responses during increased afterload have been displayed as raw data for one 0.05) with chronic hypercapnic acidosis, but remained in the physiologic range (Table 1).

Effects of Acute Hypercapnic Acidosis on Systemic Hemodynamic Function and Right Ventricular Performance (Tables 2–4, Figs. 1–4)

During acute hypercapnic acidosis, systemic hemodynamic variables (Table 2), right ventricular systolic and end-diastolic pressures, stroke work (Table 3), and RV dP/dt₅₀ (Table 4) were unchanged during acute hypercapnic acidosis. Both mean pulmonary wedge pressure and pulmonary arterial resistance were also unchanged (n = 4) during acute hypercapnic acidosis. The RV hemodynamic responses during increased afterload have been displayed as raw data for one
TABLE 4

<table>
<thead>
<tr>
<th>Effects of Hypercapnic Acidosis and Afterload on RV $dP/dt_{iso}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Moderate afterload</td>
</tr>
<tr>
<td>Peak afterload</td>
</tr>
<tr>
<td>Normocapnia ($n = 5$)</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
</tr>
<tr>
<td>$36 \pm 1$</td>
</tr>
<tr>
<td>$50 \pm 3^*$</td>
</tr>
<tr>
<td>$63 \pm 5^* \dagger$</td>
</tr>
<tr>
<td>RV $dP/dt_{iso}$ (mm Hg/sec)</td>
</tr>
<tr>
<td>$700 \pm 108$</td>
</tr>
<tr>
<td>$796 \pm 84$</td>
</tr>
<tr>
<td>$832 \pm 82^*$</td>
</tr>
<tr>
<td>Acute hypercapnic acidosis ($n = 5$)</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
</tr>
<tr>
<td>$35 \pm 3$</td>
</tr>
<tr>
<td>$44 \pm 3$</td>
</tr>
<tr>
<td>$61 \pm 5^* \dagger$</td>
</tr>
<tr>
<td>RV $dP/dt_{iso}$ (mm Hg/sec)</td>
</tr>
<tr>
<td>$710 \pm 73$</td>
</tr>
<tr>
<td>$812 \pm 89$</td>
</tr>
<tr>
<td>$925 \pm 128^*$</td>
</tr>
<tr>
<td>Chronic hypercapnic acidosis ($n = 5$)</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
</tr>
<tr>
<td>$42 \pm 2$</td>
</tr>
<tr>
<td>$54 \pm 4^*$</td>
</tr>
<tr>
<td>$62 \pm 3^* \dagger$</td>
</tr>
<tr>
<td>RV $dP/dt_{iso}$ (mm Hg/sec)</td>
</tr>
<tr>
<td>$766 \pm 116$</td>
</tr>
<tr>
<td>$782 \pm 139$</td>
</tr>
<tr>
<td>$765 \pm 168$</td>
</tr>
</tbody>
</table>

Values are expressed as means ± 1 SEM.
* Significant difference from control, $P < 0.05$.
† Significant difference between moderate and peak afterload values, $P < 0.05$.

When RV afterload was increased incrementally, RVEDP rose ($P < 0.01$) during control and acute hypercapnic acidosis (Fig. 2). However, the rate of rise (slope) in RVEDP was four times greater ($P < 0.01$) during acute hypercapnic acidosis. Moreover, the effect of combining acute hypercapnic acidosis and increased RV afterload on RVEDP was significantly greater ($P < 0.01$) than the sum of the individual effects, suggesting synergism.

Although RVEDP rose with increasing RV afterload during control and acute hypercapnic acidosis, mean arterial pressure, cardiac output (Fig. 3) and stroke volume were unchanged. RV stroke work rose ($P < 0.01$) with increasing RV afterload during control, and this relationship was preserved during acute hypercapnic acidosis (Fig. 4). RV $dP/dt_{iso}$ rose ($P < 0.05$) as RV afterload increased during control and acute hypercapnic acidosis (Table 4).

**β-Adrenergic Influence on Responses during Acute Hypercapnic Acidosis**

The response of RV $dP/dt_{max}$ to infusion of the β-agonist isoproterenol was unchanged ($P = N S$) during acute hypercapnic acidosis compared to control.

After β-adrenergic blockade with metoprolol, systemic hemodynamic function (Table 2) and RV performance (Table 3) were unchanged during control and acute hypercapnic acidosis during normal RV afterload except for RV stroke work. β-Adrenergic blockade decreased ($P < 0.05$) RV stroke work during acute hypercapnic acidosis.

During normocapnia, the rise in RVEDP (Fig. 2) with added afterload was increased 3-fold ($P < 0.01$) by β-adrenergic blockade, despite a simultaneous decrease ($P < 0.01$) in the rate of rise in RV stroke work (Fig. 4).

During acute hypercapnic acidosis, β-adrenergic blockade produced no change in the rate of rise (slope) in RVEDP with increasing afterload (Fig. 2), although the overall response was shifted upward ($P < 0.05$) and RV stroke work was shifted downward ($P < 0.05$) compared to the response prior to metoprolol (Fig. 4).

**Effects of Chronic Hypercapnic Acidosis on Systemic Hemodynamic Function and Right Ventricular Function (Tables 2-4, Figs. 1-4)**

Mean arterial pressure and pulmonary arterial pressure were unchanged following chronic hypercapnic acidosis (Table 2). In addition, mean pulmonary arterial wedge pressure was also unchanged ($n = 4$). Cardiac output and heart rate increased ($P < 0.05$) and total peripheral resistance fell ($P < 0.05$) with chronic hypercapnic acidosis. The increase in heart
Cardiac output fell during chronic hypercapnic acidosis with increased afterload in contrast to control (left panel). A significant regression response was not demonstrated for acute hypercapnic acidosis during intact sympathetic function. The cardiac output response to afterload was unchanged for all treatments following β-adrenergic blockade. *Denotes significant difference in rate of fall (slope) of cardiac output compared to control.

Figure 3. Cardiac output fell during chronic hypercapnic acidosis with increased afterload in contrast to control (left panel). A significant regression response was not demonstrated for acute hypercapnic acidosis during intact sympathetic function. The cardiac output response to afterload was unchanged for all treatments following β-adrenergic blockade. *Denotes significant difference in rate of fall (slope) of cardiac output compared to control.

Figure 2. RVEDP was maintained at nearly normal levels with increased afterload during normocapnia (control), but showed a pronounced increase during acute and chronic hypercapnic acidosis (left panel). β-Adrenergic blockade resulted in a greater increase in RVEDP with afterload during control and chronic hypercapnic acidosis (right panel). Representative 95% confidence bands are plotted around each regression line for this and subsequent figures. Although three regression lines are displayed in each panel, acute and chronic hypercapnic responses were compared separately to the control response during statistical analysis. *Denotes significant difference in rate of rise (slope) in RVEDP compared to control. †Denotes significant difference in rate of rise (slope) in RVEDP between comparable treatments before and after β-adrenergic blockade.

The present study demonstrates that hypercapnic acidosis impairs right ventricular performance during
afterload. This was reflected in an exaggerated rise in RV 
EVEDP with increasing afterload during acute and 
chronic hypercapnic acidosis. This was associated 
with a depressed stroke work response and decreased 
cardiac output with afterload during chronic hyper-
capnic acidosis, although there was no change in \( \Delta P/ \Delta t \). Responsiveness to isoproterenol was unaltered 
with hypercapnic acidosis, but \( \beta \)-adrenergic blockade 
resulted in a greater rise in RV EVEDP with increasing 
afterload during normocapnia (control) and chronic 
hypercapnic acidosis. In addition, RV stroke work 
response to increasing afterload was shifted down-
ward during control, acute, and chronic hypercapnic 
acidosis following \( \beta \)-adrenergic blockade, compared 
to responses prior to metoprolol.

The accentuated rise in RV EVEDP with increased 
afterload during hypercapnic acidosis is of interest 
and potential importance because increased RV EVEDP 
or increased systemic venous pressure has been used 
as the hallmark of RV failure in patients with lung 
disease complicated by congestive heart failure. 
Moreover, increased RV EVEDP directly relates to con-
gestive phenomena in these patients. Several explana-
tions must be entertained for the increase in 
RV EVEDP. Important compensatory mechanisms main-
taining left ventricular performance during increased 
afterload are homeometric autoregulation with aug-
mentation of contractility, and the Frank-Starling 
mechanism through increased myocardial stretch 
(Clancy et al., 1968).

Whether increased RV EVEDP with afterload during 
hypercarnic acidosis reflects diminished RV contrac-
tility is uncertain. Absence of a decrease in \( \Delta P/\Delta t \) 
suggests RV contractility was unchanged. However, 
increased preload (RV EVEDP) associated with reduced 
or unchanged stroke work during hypercapnic aci-
dosis and afterload suggests decreased contractility. 
Reasons for this discrepancy are unclear. RV stroke 
work and preload did vary, suggesting that a 
“Starling” analysis might be useful in the present 
study. However, this could not be done, since no 
protocols were performed where RV stroke work was 
determined with primary manipulation of RV pre-
load. Future investigations of this type may provide 
insight into the RV dysfunction in the present study.

Because of the discrepancy, we considered other 
explanations for the rise in RV EVEDP. RV EVEDP may 
have increased simply because of augmented venous return 
to the RV through either increased total blood volume 
or vascular capacitance changes. Unfortunately, we 
have no direct evidence on these points.

Since the sympathetic nervous system seems to 
play an important compensatory role in opposing the 
cardiac effects of hypercapnia (Brown and Miller, 
1952; Nahas and Cavert, 1957), we wondered if it 
might be altered. Previous investigators have mea-
sured increased circulating catecholamines during 
acute hypercapnic acidosis (Morris and Miller, 1962; 
Tenney, 1956), although Kohler et al. (1972) observed 
unchanged plasma norepinephrine and epinephrine 
concentrations during acute hypercapnic acidosis in 
anesthetized dogs. The unchanged myocardial re-
response to isoproterenol infusion during hypercapnic 
acidosis differs from past studies, which have ob-
served diminished responsiveness to isoproterenol 
during acute hypercapnic acidosis (Page and Olm-
stead, 1951; Tenney, 1956; Atkinson and Rand, 1972). 
However, most of these studies were in species other 
than dogs, the hypercapnic acidosis was more severe, 
anesthetic agents were used, and the myocardial re-
response to catecholamine administration was not 
measured.

The results of \( \beta \)-adrenergic blockade indicate that the 
\( \beta \)-adrenergic component of the sympathetic ner-
vous system is important in the RV response to 
afterload. Support for this can be found in the steeper 
rate of rise in RV EVEDP with applied afterload during 
control and chronic hypercapnic acidosis during \( \beta 
\)-adrenergic blockade. The greatest rate of rise in 
RV EVEDP with increasing afterload occurred with 
chronic hypercapnic acidosis following \( \beta \)-adrenergic 
blockade. This is further evidence suggesting that 
chronic hypercapnic acidosis resulted in impairment 
of right ventricular function during increased after-
load. Since RV responses to afterload during control 
with \( \beta \)-adrenergic blockade resemble hypercapnic re-
ponses prior to metoprolol, this suggests that dimin-
ished \( \beta \)-adrenergic activity could contribute to the RV 
dysfunction with afterload during hypercapnia. Al-
though RV responses to isoproterenol were unaltered 
during hypercapnia, it is possible that diminished 
cardiac catecholamine release could have occurred 
during hypercapnic acidosis.

We also considered the possibility that hyperpnea 
contributed to diminished RV function. Hyperpnea 
may have contributed to increased venous return to 
the RV, but this should have led to augmented cardiac 
performance. This is supported by observations of 
Kontos et al. (1965) that hyperpnea was responsible 
for a major component of the circulatory response 
during acute hypoxemia in anesthetized dogs. When 
the hyperpnea was abolished during hypoxia, and 
ventilation was controlled, the increases in cardiac 
output and heart rate and decrease in systemic vas-
cular resistance were abrogated. However, Vatner and 
Rutherford (1978) observed that hyperpneic stimula-
tion of the pulmonary inflation reflex from carotid 
body stimulation with nicotine opposed increased 
mean arterial pressure and left ventricular \( \Delta P/\Delta t \). 
When stimulation of the pulmonary-inflation reflex 
was blocked by controlled ventilation, mean arterial 
pressure and left ventricular \( \Delta P/\Delta t \) responses were 
heightened with nicotine stimulation of the carotid 
body. Since hypercapnic acidosis stimulates the 
carotid body (Heymans and Neal, 1958), it is possible 
that hyperpnea in the present study may have op-
posed the systemic pressor and RV contractile re-
sponses during hypercapnic acidosis through the pul-
monary inflation reflex. However, since the degree of 
hyperpnea was comparable during acute and chronic 
hypercapnic acidosis, it is unlikely that the pulmonary 
reflex was responsible for the different RV \( \Delta P/\Delta t \)
response during acute vs. chronic hypercapnic acidosis.

The results of the present study vary from past investigations which have confined themselves to acute hypercapnic acidosis in the normally after-loaded heart. Hypercapnic acidosis has clearly resulted in reduced cardiac performance in the isolated heart preparation, with resultant cardiac dilation and decreased cardiac output, stroke volume, and amplitude of contraction (Jerusalem and Starling, 1910; Nahas and Cavert, 1957; McElroy et al., 1958). Studies in anesthetized open-chest dogs with 8 to 10% CO₂ have also revealed a reduction in heart rate and contractile force (Boniface and Brown, 1953) and a fall in stroke work (Monore et al., 1960).

However, in conscious animal studies where the methodological problems of anesthetic agents with cardiac depressant properties and mechanical ventilation have been avoided, exposure to CO₂ has resulted in transient and insignificant effects on cardiac performance. Six percent CO₂ resulted in transient elevation of right and left atrial pressures and a fall in cardiac output in the first 20 minutes, which disappeared after 30 minutes of exposure (Horwitz et al., 1968). In a similar study, mild increases in PaCO₂ of 12 mm Hg resulted in a diminished maximum acceleration of aortic blood flow which rapidly disappeared after the onset of hyperpnea and tachycardia (Noble et al., 1966). The present study differs from previous conscious animal studies in that we studied the afterload-stressed ventricle which appears to unmask the deleterious cardiac effects of hypercapnic acidosis.

Previous investigators have observed diminished left ventricular function with acidosis in the isolated perfused guinea pig heart preparation (McElroy et al., 1958), and in anesthetized mechanically ventilated dogs (Bierholm et al., 1975) and cats (Downing et al., 1966) during constant heart rate, cardiac output, and aortic pressure. The present study does not clarify the roles of acidosis vs. increased carbon dioxide tension per se, since the chronic hypercapnic acidosis was incompletely compensated after 2 weeks duration. Even if the intravascular pH had been normal, the possibility of intracellular acidosis would exist because of the diffusability of CO₂. Lack of complete compensation with chronic hypercapnia is consistent with previous studies. In a similar study in which dogs were exposed to 5% CO₂ for 2 weeks, there was only partial compensation for the respiratory acidosis (Jennings and Chen, 1976). In addition, ventilation remained elevated, although it was lower than the level observed with acute hypercapnia.

The PaCO₂ levels in the 70's during control are probably related to the altitude of Denver since we have observed comparable Pao₂ values during previous investigations in conscious dogs (Rose et al., 1982). Comparable Pao₂ levels during acute hypercapnic acidosis are indirectly related to altitude, since N₂ was added to inspired air during acute hypercapnic acidosis to maintain the FeO₂ and hence the PaO₂ at control levels. These levels of PaO₂ are within the physiological range. Moreover, since RV performance during afterload was compromised during chronic hypercapnic acidosis when the Pao₂ was 88 ± 2 mm Hg, it is very unlikely that the PaO₂ played any role in altered RV function.

We have previously observed increased mean arterial pressure, heart rate, and cardiac output and diminished systemic vascular resistance during comparable acute hypercapnic acidosis in conscious dogs (Rose et al., 1982). The absence of change of these variables during acute hypercapnic acidosis in the present study may in part be related to cardiac pacing with abrogation of increased heart rate during acute hypercapnic acidosis. However, it is also possible that these variables might have changed significantly with increased number of observations.

Yaron and Bennett (1978) observed normal mean arterial pressure and cardiac output in conscious dogs when applied afterload with the balloon occlusion catheter resulted in RV systolic pressures of 66 ± 4 mm Hg. In agreement, our study observed comparable RV pressures during acute afterloading using the balloon occlusion catheter, while systemic hemodynamic function remained stable. However, with comparable afterload during normocapnia in conscious dogs, Yaron and Bennett (1978) observed a greater increase in RVEDP (7 ± 1 mm Hg) compared to the present study (4 ± 1 mm Hg). The blunted rise in RVEDP in the present study may be due to the fact that afterload was increased gradually and incrementally in contrast to the rapid one-step increase in afterload by Yaron and Bennett.

In summary, this investigation has studied the separate and combined effects of hypercapnic acidosis and afterload on RV performance. Although neither, alone, adversely affected function of the RV, their combination resulted in diminished RV performance. Although the mechanisms responsible for increased RVEDP are unclear, this study suggests that hypercapnic acidosis may contribute to the occurrence of congestive heart failure in patients with CO₂ retention and pulmonary hypertension.

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INDEX TERMS: Hypercapnic acidosis · Right ventricle · Right ventricular afterload · Right ventricular dysfunction · Sympathetic nervous system · β-adrenergic blockade
Right ventricular performance during increased afterload impaired by hypercapnic acidosis in conscious dogs.


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