EFFECTS OF ACUTELY INDUCED CHANGES IN ARTERIAL pH ON PULMONARY VASCULAR RESISTANCE DURING NORMOXIA AND HYPOXIA IN AWAKE DOGS

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SUMMARY

1. Awake dogs with chronically implanted catheters (pulmonary artery, left atrium, aorta) and electromagnetic flow probe (main pulmonary artery) underwent five types of experiments in succession: (1) slow infusion of 0.4 M-hydrochloric acid; (2) rapid infusion of 1.0 M-sodium bicarbonate; (3) exposure to 30 min of hypoxia (10% O₂); (4) exposure to hypoxia after arterial pH had been lowered to 7.30; (5) exposure to hypoxia after pH had been increased to 7.55. Intravascular pressures, pulmonary vascular resistance, cardiac output, arterial gas tension and pH were studied.

2. Acute acidosis (pH 7.21) resulted in a small rise in pulmonary artery pressure, cardiac output and pulmonary vascular resistance, associated with a decrease in $P_{a,CO_2}$. Acute alkalosis (pH 7.61) was accompanied by a small rise in pulmonary artery pressure, marked increase in cardiac output, a fall in pulmonary vascular resistance and mild elevation in $P_{a,CO_2}$. During acidosis hypoxia resulted in a more pronounced rise in pulmonary vascular resistance than during alkalosis ($P < 0.01$).

3. The study provides evidence that in the intact, awake dog with its compensatory mechanisms acute alkalosis decreases pulmonary vascular resistance by decreasing vascular tone and/or recruitment of pulmonary vascular channels; it diminishes the vasoconstrictive response to hypoxia; conversely, mild acidosis increases the pulmonary vascular resistance slightly and enhances vasoconstriction during hypoxia to a small extent.

Key words: hypoxia, acidosis, alkalosis, pulmonary vascular resistance, lung.

The dependence of pulmonary vascular resistance (PVR) on arterial pH has been studied in anaesthetized dogs (Bergofsky, Lehr & Fishman, 1962; Shapiro, Simmons & Linde, 1966), newborn calves (Rudolph & Yuan, 1966; Silove, Inoue & Grover, 1968), perfused cat lungs (isolated and/or in situ) (Barer, Howard & McCurrie, 1967; Viles & Shepherd, 1968), isolated dog lungs (Lloyd, 1966), and to a much lesser extent in healthy human subjects (Bergofsky et al., 1962) or patients with chronic pulmonary disease (Enson, Giuntini, Lewis, Morris, Ferrer

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In all these studies excepting Housley's work an increased PVR was observed during acidosis. A corresponding decrease in PVR during alkalosis was reported by Barer et al. (1967) and Shapiro et al. (1966); Bergofsky et al. (1962) and Enson et al. (1964) found that in human subjects pulmonary arterial pressure either fell or rose with rising pH. Silove et al. (1968) did not observe a change in PVR during acutely induced alkalosis.

These data, with the exception of the group of healthy subjects studied by Bergofsky et al. (1962) during mild alkalosis, were obtained in patients with chronic lung disease or in animals under a variety of experimental restrictions to eliminate variables. For instance, normal spontaneous respiration has been replaced by positive-pressure ventilation to avoid respiration-induced changes in pH; anaesthesia has been used to allow convenient experimentation; lungs isolated or perfused in situ to minimize dependent variables. Yet such experimental restrictions are known to mask or alter physiological phenomena that operate in the truly intact organism.

The vasoconstrictive response to hypoxia which is so apparent in the unanaesthetized human subject (Fishman, Fritts & Cournand, 1960; Storstein, 1952) and dog (Thilenius, Hoffer, Fitzgerald & Perkins, 1964), may be found not at all or only to a much smaller extent in open chest animals (Aviado, Cerletti, Alanis, Bulle & Schmid, 1957; Rivera-Estrada, Saltzman, Singer & Katz, 1958; Rodbard & Harasawa, 1959), and is distinctly altered even by anaesthesia alone in spontaneously breathing dogs (Thilenius, 1966). After an alteration of arterial pH and Po_2 new levels are attained for ventilation, Pco_2, intrapleural pressure and related variables and are part of the total physiological response.

To obtain results relating this integrated response of the animal to a physiological stimulus we have used the awake trained dog, a technique with which we have collected in the past a substantial fund of normal information (Thilenius et al., 1964; Thilenius, Candiolo & Beug, 1967; Thilenius & Derenzo, 1969). In the present study we examined changes in pulmonary vascular resistance over an arterial pH range of 7.21–7.61, superimposing hypoxia as a vasoconstrictive stimulus on acidosis, the normal acid–base state and alkalosis.

**METHODS**

Unanaesthetized dogs with chronically implanted vinyl catheters in pulmonary artery, left atrium and aorta, an electromagnetic flow transducer (Biotronex BL410) around the main pulmonary artery, and a chronic tracheostomy were studied. Two weeks after the surgical procedures the dog was placed on its left side on an experimental table. The trachea was intubated via the tracheostomy; the catheters were connected to Statham P23Db strain gauges, mid-chest level being zero reference. ECG electrodes and a rectal thermistor thermometer were applied. Inspiratory gas was mixed as needed and continuously analysed with a Beckman C-2 oxygen analyser just before entering a low resistance respiratory valve. Inspiratory and expiratory CO_2 tensions were continuously monitored (Beckman LB–1 gas analyser), sampling directly from the tracheal tube. All results were recorded with a Sanborn photographic recorder.

Hypoxia-induced haemodynamic changes reached a maximum within 1–5 min, usually with no further change throughout the 30 min of hypoxia; in a few experiments vascular pressures and blood flow tended to return toward control values after the 15 min. Hypoxia results in this report were therefore observed during the steady state of the 6th to 15th min of hypoxia.
Acidosis series

Five dogs (one male, four female; weight 12.7–21.4 kg, average 17.4 kg) underwent each of the following types of experiments one to three times: (1) exposure to acute hypoxia (10% O₂) after a 20 min control period of breathing ambient air (eight experiments); (2) infusion of 0.4 M-HCl (60–120 mEq, average 90 mEq) into the main pulmonary artery at a rate of 3 ml/min until arterial pH had fallen to approx. 7.20 (six experiments); (3) infusion of 0.4 M-HCl (40–80 mEq, average 60 mEq) until arterial pH had been lowered to 7.30; acute hypoxia (10% O₂) was then superimposed for 30 min during which an additional 20–80 mEq (average 30 mEq) of H⁺ was infused (eight experiments). With two exceptions, each individual dog participated in the same number of experiments with each group to avoid bias that might be caused by an exceptional response of a given animal. The same applies to the alkalosis series.

Alkalosis series

Four male dogs (weight 8.2–15.9 kg, average 12.0 kg), none of which had participated in the acidosis experiments, underwent each of the following three types of experiments one to three times: (1) exposure to acute hypoxia as described for the acidosis series (seven experiments); (2) infusion of 1.0 M-NaHCO₃ (90–120 mEq, average 95 mEq) into the main pulmonary artery until arterial pH had risen to approx. 7.60 (seven experiments); infusions were given in 10–30 ml (fractions) every 5–10 min at a rate of 10–30 ml/min; (3) exposure to acute hypoxia after arterial pH had been increased to 7.55 by infusing 1·0 M-NaHCO₃ (40–55 mEq, average 50 mEq) (nine experiments).

The effect of hypertonicity on cardiac output and pulmonary vascular resistance was studied in two dogs by infusion of 30 ml amounts (rate 50–60 ml/min) of 1.0 M-NaHCO₃ or 30% (w/v) dextrose in water (eight experiments each); both solutions have an osmolar concentration approximately 6 times that of plasma.

Arterial blood for gas analysis (Instrumentation Laboratory Blood Gas Analyser 113) was obtained intermittently. Intravascular pressures, ECG, respiratory CO₂ tension from tracheal cannula (thereby respiratory frequency), and pulmonary blood flow were constantly monitored and recorded every 5 min. Each dog was studied over a 4–6 week period and subsequently killed to confirm proper catheter and blood flow transducer placement.

Calculations

All intravascular pressures were measured during end-tidal expiration to minimize differences secondary to different degrees of depth of inspiration. The pressure gradient used for calculation of pulmonary vascular resistance (mean pulmonary arterial minus mean left atrial pressure) might differ from some reported studies but probably reflects changes in the active control of the pulmonary vasomotor tone more reliably. The single end-hole of the pulmonary artery catheter faced upstream, measuring ‘head on’ pressure. For the electromagnetic flow signal, the relatively flat segment of diastole of the phasic pulmonary flow was used as zero flow and recorded immediately before the mean flow tracing. Mean blood flow was measured during end-tidal expiration. The flow meter was calibrated by simultaneously recording dye-dilution curves and the electromagnetic flow signal. Significance levels were calculated with the Student t test; P values <0.01 were taken as significant. Body surface area (BSA) was estimated by using Benedict’s formula for dogs over 4 kg weight: BSA (cm²) = 11.2 (weight in g)²/³.
RESULTS

The acidosis and alkalosis experiments were conducted sequentially, and different animals participated in the two groups. The respective control haemodynamic values are, therefore, somewhat different in the two groups (Table 1), but are consistent within each group. The main differences between the two groups are: the animals in the alkalosis group have a higher control pulmonary artery pressure, an equal or slightly lower cardiac output, and a higher pulmonary vascular resistance than those in the acidosis group. Because of these differences, the haemodynamic data observed during hypoxia, acidosis and alkalosis have been expressed in the figures and text as percentages of the control value, whereas absolute values are given in Table 1. Comparisons between the two groups are based on the percentage results. To

<table>
<thead>
<tr>
<th>Group</th>
<th>1. Hypoxia</th>
<th>2. pH change</th>
<th>3. pH change + hypoxia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Test</td>
<td>Control</td>
</tr>
<tr>
<td>A</td>
<td>PPA</td>
<td>14.9 ± 1.0</td>
<td>* 20.0 ± 1.5</td>
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<tr>
<td>B</td>
<td>19.0 ± 1.7</td>
<td>* 25.4 ± 1.7</td>
<td>19.3 ± 1.6</td>
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<tr>
<td>A</td>
<td>CI</td>
<td>4.04 ± 0.24</td>
<td>* 4.36 ± 0.27</td>
</tr>
<tr>
<td>B</td>
<td>3.18 ± 0.24</td>
<td>* 3.42 ± 0.22</td>
<td>3.73 ± 0.19</td>
</tr>
<tr>
<td>A</td>
<td>PVR</td>
<td>188 ± 26</td>
<td>* 297 ± 38</td>
</tr>
<tr>
<td>B</td>
<td>335 ± 40</td>
<td>* 502 ± 54</td>
<td>272 ± 31</td>
</tr>
<tr>
<td>A</td>
<td>PLA</td>
<td>5.5 ± 0.5</td>
<td>* 4.1 ± 0.5</td>
</tr>
<tr>
<td>B</td>
<td>5.7 ± 0.8</td>
<td>* 4.5 ± 0.4</td>
<td>6.5 ± 0.7</td>
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<tr>
<td>A</td>
<td>Pa,02</td>
<td>89 ± 2</td>
<td>* 41 ± 1</td>
</tr>
<tr>
<td>B</td>
<td>80 ± 4</td>
<td>* 37 ± 2</td>
<td>85 ± 3</td>
</tr>
<tr>
<td>A</td>
<td>Pa,CO₂</td>
<td>33 ± 1</td>
<td>* 24 ± 1</td>
</tr>
<tr>
<td>B</td>
<td>33 ± 1</td>
<td>* 23 ± 1</td>
<td>32 ± 1</td>
</tr>
<tr>
<td>A</td>
<td>pH₄</td>
<td>7.385 ± 0.005 * 7.493 ± 0.008</td>
<td>7.391 ± 0.002 * 7.211 ± 0.015</td>
</tr>
<tr>
<td>B</td>
<td>7.431 ± 0.008 * 7.529 ± 0.017</td>
<td>7.426 ± 0.005 * 7.605 ± 0.013</td>
<td>7.547 ± 0.015 * 7.621 ± 0.011</td>
</tr>
</tbody>
</table>

* PA = pulmonary artery pressure, mean (mmHg); CI = Cardiac index (lmin⁻¹ m⁻²); PVR = pulmonary vascular resistance (dyn.s.cm⁻⁵/m²); PLA = left atrial pressure, mean (mmHg).
† Data after alteration of pH, but before superimposition of hypoxia.

convey the spread of our results, Fig. 1 depicts the results of each acidosis and alkalosis experiment; graphs for the other experimental groups demonstrated similarly consistent patterns. The reason for the differences in control data for the two groups is not known; it is probably not related to the different weights or sexes of the animals but rather to individual variation as well as the inhomogeneous breed of the dogs.

Since this study uses two primary experimental variables, PO₂ and pH, two sets of control data are required. The first set involves the response to hypoxia only, the second set the
response to altered pH only. The results of combined alteration of pH and P\textsubscript{O\textsubscript{2}} are interpreted against this background.

**Response to hypoxia**

During the period of hypoxia \( \text{Pa}_\text{O}_2 \) fell to 41 mmHg for the acidosis group, to 37 mmHg for the alkalosis group (Table 1), associated with a fall in \( \text{Pa}_\text{CO}_2 \) from 33 to 24 and 23 mmHg respectively; concomitantly, arterial pH rose 0·11 and 0·10 units respectively. This degree of hypoxia resulted for both groups in a significant rise (\( P < 0·01 \)) in pulmonary artery pressure (35\%) and in pulmonary vascular resistance (60\%). Cardiac output rose 8\%, and left atrial pressure fell slightly. The respective changes in mean values and standard error in the two groups were virtually identical. A statistically significant difference in the response of the two groups to hypoxia did not exist.

Fig. 1. Changes in haemodynamic measurements for acidosis and alkalosis, expressed as percentages of the control value. ——, Individual experiments; ---, group averages. Origin and head of arrows indicate initial and final values.
Response to acidosis and alkalosis

Acidosis. Decrease in arterial pH from 7.39 to 7.21 resulted in a small rise in pulmonary artery pressure (14%) and pulmonary vascular resistance (27%) (Table I); these changes had \( P \) values <0.05, and represent only a suggestive trend (see Figs. 1–4). Cardiac output tended to increase slightly (Fig. 1), whereas changes in left atrial pressure were variable. This degree of acidosis increased respiration to an extent that \( PaO_2 \) rose from 89 to 99 mmHg, with an associated fall in \( PaCO_2 \) from 31 to 27 mmHg.

![Graph](image)

**Fig. 2.** Effect of (a) acidosis and (b) alkalosis on pulmonary artery pressure, expressed as percentages of control pressure. ○, Control values; ●, mean values obtained during normoxia and after alteration of pH; ▲, mean values during hypoxia. Bars represent ±SEM.

Alkalosis. When arterial pH was increased from its control value of 7.43 units to 7.61 (Table I), \( PaO_2 \) fell from 85 to 79 mmHg and \( PaCO_2 \) rose from 32 to 38 mmHg. This degree of alkalosis, induced by hyperosmotic NaHCO\(_3\), resulted in a rise \((P<0.01)\) in pulmonary artery pressure (10%), cardiac output (30%), and left atrial pressure (25%), but a fall \((P<0.01)\) in pulmonary vascular resistance (19%) (Figs. 2–4); these changes were most pronounced immediately after the injection of NaHCO\(_3\), and returned toward control values within 5–10 min. When the two groups were compared (response to acidosis versus alkalosis), the rise in pulmonary artery pressure observed in both groups was not different whereas the respective change in cardiac output and pulmonary vascular resistance had \( P \) values <0.01.

Effects of hypertonicity

Infusion of 30 ml of 1·0 m-NaHCO\(_3\) (real osmolarity 1800 mm) at a rate 2–3 times faster than for the remaining study, resulted in a 40% increase in cardiac output; this maximum
Pulmonary vascular resistance, pH and hypoxia

FIG. 3. Effect of (a) acidosis and (b) alkalosis on pulmonary blood flow, expressed as percentages of the control flow. ○, Control values; ●, mean values obtained during normoxia and after alteration of pH; ▲, mean values during hypoxia. Bars represent ±SEM.

FIG. 4. Effect of (a) acidosis and (b) alkalosis on pulmonary vascular resistance, expressed as percentages of control resistance. ○, Control values; ●, mean values obtained during normoxia and after alteration of pH; ▲, mean values during hypoxia. Bars represent ±SEM.
value was attained approx. 100 s after onset of injection. There was a concomitant increase in pulmonary artery–left atrial pressure gradient (15%) and a decrease in pulmonary vascular resistance (19%); heart rate rose 30%. These changes were transient, lasting not longer than 3–4 min. After equally rapid infusion of 30% dextrose in water (real osmolarity 1700 mm) cardiac output rose 74%, the pulmonary artery–left atrial pressure gradient 23% and heart rate 63%, whereas pulmonary vascular resistance decreased 30%.

**Hypoxia superimposed on acidosis or alkalosis**

**Acidosis.** In these experiments hypoxia (10% O₂) was superimposed on relatively mild acidosis (pH 7-30) (Table 1). The degree of hypoxia was the same (PaO₂ 40 mmHg) as for the hypoxia control experiments with normal pH. The circulatory response to hypoxia in this acidotic group was qualitatively the same as for the control (normal pH) experiments. Quantitatively, the hypoxia-induced rise in pulmonary artery pressure (41%), cardiac output (13%) and pulmonary vascular resistance (79%) was slightly higher than for the control experiments, but this difference was not significant. The fall in left atrial pressure (32%) was similar to the control experiments.

**Alkalosis.** When hypoxia was superimposed on alkalosis (pH 7-55), a small rise in pulmonary artery pressure (11%, P<0.01), cardiac output (9%, P<0.05) and pulmonary vascular resistance (30%, P<0.01) was observed (Table 1). In comparison with the hypoxia control response (normal pH), the rise in pulmonary artery pressure and pulmonary vascular resistance was slightly less (P<0.025 and <0.10 respectively) for the alkalotic dog. The increase in cardiac output (9%) was of the same magnitude as for the hypoxia control experiments. Comparing the quantitative responses to hypoxia of the acidotic against the alkalotic group, the rise in pulmonary artery pressure and pulmonary vascular resistance was significantly lower (P<0.01) for the alkalotic animal whereas the cardiac output rose to a similar degree for both groups.

Figs. 2–4 give a graphical summary of the observed changes in circulatory changes for the control experiments as well as for the combined hypoxia–pH experiments.

**DISCUSSION**

The purpose of this paper was to study the integrated response of the unsedated awake adult dog to alteration of arterial pH and PaO₂. We chose the dog because its response to hypoxia and acidosis, as judged from previous studies, is similar to the human subject. Our study differs from others by avoiding anaesthesia and sedation, by allowing normal spontaneous respiration and by superimposing hypoxia on different pH values. We have not attempted to maintain PaCO₂ constant when pH was altered or during hypoxia, because we did not want to mask physiological compensatory mechanisms, such as the opposing actions of acidosis and CO₂ on pulmonary vascular resistance (Viles & Shepherd, 1968). Accordingly, the results of this study represent net effects observed after acute alteration of arterial pH and PaO₂. As in other studies (Enson et al., 1964; Shapiro et al., 1966; Viles & Shepherd, 1968; Bergofsky et al., 1962; Harvey et al., 1967; Housley et al., 1970) changes in arterial pH were induced by infusion of hyperosmotic solutions, 0.4 M-HCl being 2-4 times iso-osmotic and 1.0 m-NaHCO₃ being 6 times iso-osmotic. These concentrated solutions were used to avoid excessively large infusions; for instance administration of 100 mEq of NaHCO₃ in iso-osmotic solution would represent 600 ml of fluid, to be given over a 20–30 min period. For technical reasons we did not
Pulmonary vascular resistance, pH and hypoxia

succeed in doing both acidosis and alkalosis experiments in the same animal. Therefore we had to compare two groups of dogs with slightly different control values and express induced changes in pressures, flow and resistance in relation to the co-ordinated control value. It may be argued that this method of analysis produces spurious $P$ values. However, when we based the statistical analyses within each group on the actual results (Table 1) rather than the percentage results we obtained identical $P$ values.

The response to hypoxia at a normal arterial pH was identical for both groups of animals and consisted of a significant rise in pulmonary artery pressure and pulmonary vascular resistance ($P<0.01$), with only a small increase in cardiac output. This response is not different from results reported previously for the same animal preparation (Thilenius et al., 1967; Thilenius & Derenzo, 1969) and for human subjects (Fishman et al., 1960; Storstein, 1952); only the subjects used by Housley et al. (1970) did not show any change in pulmonary vascular resistance during breathing of 12–13% oxygen.

For the acidosis group a decrease in arterial pH from 7.39 to 7.21 resulted in a small increase in pulmonary artery pressure ($P<0.05$), in cardiac output ($P<0.25$) and in pulmonary vascular resistance ($P<0.05$). This absence of statistical significance may be related to the relatively small number of experiments or more likely to the relatively mild degree of acidosis. The same explanation probably applies to the studies of Housley et al. (1970) who, using still milder acidosis (pH 7.293), did not observe a significant change in pulmonary vascular resistance, but only a mild increase in pulmonary artery pressure and cardiac output. Other investigators, using more severe degrees of acidosis (Bergofsky et al., 1962; Shapiro et al., 1966; Rudolph & Yuan, 1966; Barer et al., 1967; Viles & Shepherd, 1968) have reported that pulmonary vascular resistance rises more steeply between pH 7.2 and 6.8. Rudolph & Yuan (1966) and Viles & Shepherd (1968) have described a curvilinear dependence of pulmonary vascular resistance on pH, and it seems that we have observed in our dogs only the relatively flat segment between pH 7.4 and 7.2. An additional reason for our small rise in pulmonary vascular resistance with acidosis may be the use of normal respiration in this study (all other animal studies use positive-pressure ventilation). Positive-pressure ventilation may limit the applicability of the pulmonary artery–left atrial pressure gradient for resistance calculations; further, it may preclude possible compensatory mechanisms which tend to lower pulmonary vascular resistance, such as increased depth of respiration during acidosis.

The response to alkalosis (pH 7.61) was characterized by a small rise in pulmonary artery pressure of approximately the same magnitude as that seen with acidosis, associated with a marked rise in cardiac output and, consequently, a fall in pulmonary vascular resistance ($P<0.01$); the rise in cardiac output was brought about by an increase in heart rate ($P<0.025$) and stroke volume ($P<0.025$). Since left atrial pressure rose to the same extent as pulmonary arterial pressure, a passive recruitment of pulmonary vascular channels probably also occurred. These results for NaHCO$_3$-induced alkalosis, particularly the rise in cardiac output, are comparable to those of Enson et al. (1964) on patients with chronic pulmonary disease and Bergofsky et al. (1962) on normal human subjects, and are also similar to the results of Shapiro et al. (1966) on positive-pressure-ventilated dogs. When isolated lung lobes were perfused with constant flow a fall in pulmonary artery pressure (and thus pulmonary vascular resistance) was noted by Barer et al. (1967), but absence of change was reported by Silove et al. (1968). Whereas the alkalosis-related decrease in pulmonary vascular resistance could be explained as a direct effect of the hydrogen ion on pulmonary arterial vessels, the rise in cardiac output might
have a separate explanation, and is most likely related to the hyperosmoticity of the administered NaHCO₃ solution. This increase in cardiac output which accompanies increased osmoticity of intravascular fluid is independent of pH and presumably related to peripheral vasodilatation. It is found to an even larger extent during infusion of 30–50% dextrose solutions or radiographic contrast media.

Exact interpretation of the observed decrease in pulmonary vascular resistance after bicarbonate infusion is therefore not possible since increase in pH and plasma osmolar concentration occurred simultaneously. It can only be said that the observed responses were, with one exception (Aviado et al., 1957), qualitatively and quantitatively similar to other reports in quite different experimental circumstances.

The response to hypoxia was different for the alkalotic and acidotic state. For the alkalotic dog the rise in pulmonary artery pressure and pulmonary vascular resistance was significantly smaller (P<0.01) than for the acidotic dog, but the increase in cardiac output was approximately the same. In view of the experiments with acidosis and alkalosis alone, this result is not surprising; it supports Rudolph & Yuan (1966) who reported an enhanced vasoconstrictive response to hypoxia for acidosis. Lloyd (1966), using perfused lung lobes, found diminution of the hypoxic constrictor response when the pH of the perfusate was increased from 7.40 to 7.60. Silove et al. (1968) did not observe this blunting of the hypoxic response, probably because the rise in pH (7.46–7.56) was too small to obtain a significant difference.

Our study provides evidence that even in the intact awake adult dog with all its regulatory and compensatory mechanisms, alkalosis induced by 1.0 M-NaHCO₃ results in a decrease in pulmonary vascular resistance and diminishes the vasoconstrictive response to hypoxia; it is not known whether this effect is primarily due to the increase in pH or in osmolar concentration. Acidosis of relatively mild degree enhances hypoxic pulmonary vasoconstriction to a small extent.

**ACKNOWLEDGMENTS**

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Pulmonary vascular resistance, pH and hypoxia


