The Relationship of Respiratory Failure to the Oxygen Consumption of, Lactate Production by, and Distribution of Blood Flow Among Respiratory Muscles during Increasing Inspiratory Resistance

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ABSTRACT An animal model was developed to determine if blood flow to the respiratory muscles limits oxygen delivery and thus work output during inspiratory resistance. With incremental increases in the rate of work of breathing to 15 times the resting level, blood flow to the diaphragm rose exponentially 26-fold. Blood flow to other inspiratory and a few expiratory muscles increased to a much smaller extent, often only at the greater work loads. Cardiac output and blood pressure did not change. Arterial-venous oxygen content difference across the diaphragm became maximal at low work rates and thereafter all increases in oxygen delivery during higher work rates were accomplished by increments in blood flow. Oxygen consumption of the respiratory musculature calculated by blood flow times oxygen extraction increased exponentially with increasing work of breathing and was less than the increase in total body oxygen consumption at each work load. Hypoxemia and respiratory acidosis occurred when the animals inspired through the highest resistance; blood flow and oxygen consumption were even higher than that observed during previous resistances and there was no evidence of a shift to anaerobic metabolism in blood lactate and pyruvate levels. Respiratory failure did not appear to be a consequence of insufficient blood flow in this model.

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INTRODUCTION

The factors which limit the ability to maintain increased rates of respiratory muscle work are not known. One metabolic limitation might be oxygen delivery to the respiratory muscles, since anaerobic metabolism is much less efficient in generating energy. There may be a maximum blood flow to the respiratory muscles which sets an upper limit on oxygen delivery and thus on the rate of energy expenditure. Furthermore, the efficiency of oxygen utilization in generating work output by respiratory muscles may decrease as more isometric work is required to generate tension to overcome a resistance load. The combination of these factors would set a limit on work output.

Our purpose in the present investigation was to determine the changes in blood flow, oxygen delivery, and efficiency of the respiratory muscles as increasing resistance loads were imposed and to determine whether a sharp increase in anaerobic metabolism occurs before the earliest evidence for respiratory failure. The latter finding would be expected if a limit in oxygen delivery to muscles of respiration is an important source of respiratory failure.

METHODS

Plethysmograph. Seven healthy mongrel dogs weighing 16–27 kg were anesthetized with sodium pentobarbital 25 mg/kg intravenously; small increments were given subsequently to sustain adequate anesthesia but maintain the corneal reflex. A tracheostomy was performed and the tracheostomy tube connected to a one-way Otis-McKerrow valve. An intraesophageal balloon was positioned in the distal esophagus and inflated with 1.0 ml of air, a volume which had been shown to allow accurate measurement of externally applied pressure from +50 to −50 cm H_2O. The animal was then placed supine in a pressure-compensated flow

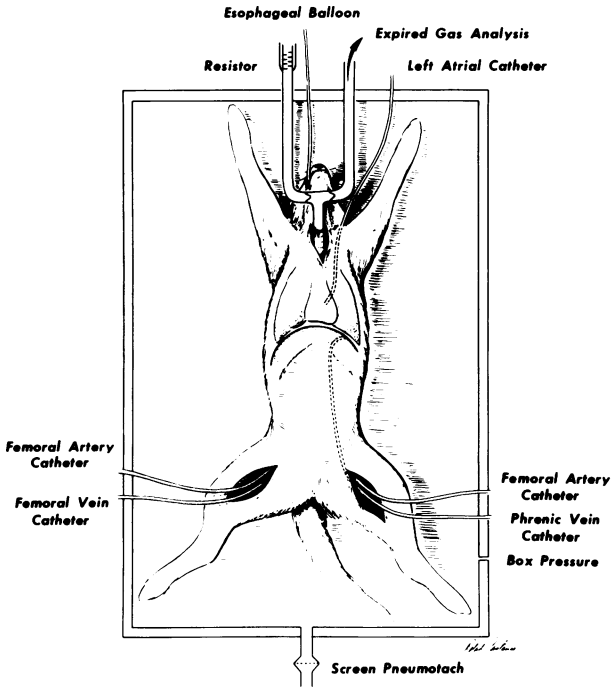

FIGURE 1 Animal preparation. Instrumentation of the experimental animal is demonstrated in this sketch of the dog inside the pressure-compensated volume plethysmograph breathing to the outside through a one-way valve inspiring through a resistor and exhaling through low resistance tubing. An esophageal balloon is in place, and catheters are present in the left atrium, both femoral arteries, right femoral vein, and left inferior phrenic vein.

plethysmograph (Fig. 1). It breathed to the outside of the box through separate, noncompressible, large bore inspiratory and expiratory tubes. Flow was measured as pressure drop across the screen pneumotachygraph (400 mesh, diameter 4.0 cm) and pressure was measured with a Validyne DP-45 transducer (Validyne Engineering Corp., Northridge, Calif.). Pressure compensation was accomplished by subtracting that fraction of the box pressure signal from the integrated box flow signal required to close the loop formed by plotting the esophogeal balloon pressure signal against the integral of the flow signal of the *x-y* coordinates of an oscilloscope screen while forcing a sine wave volume signal into the box and simultaneously into a bottle containing the esophageal balloon. This was adjusted before each experiment with styrofoam blocks inside the box of a size approximately equal to that of the experimental animal. The plethysmograph had a flat amplitude response and was in phase with the esophageal balloon to at least 8 cps. Because of free exchange of air across the screen pneumotachygraph, temperature inside the box never exceeded 2°C above that outside despite the box being otherwise closed throughout the experiment.

Work of breathing. Esophageal pressure was measured with a Statham PM131TC transducer (Statham Instruments Div., Gould Inc., Oxnard Calif.). With a Sanborn Ampex Model 2000 recorder (Ampex Corp., Redwood City, Calif.), pressure and plethysmographic thoracic gas volume were recorded simultaneously on electromagnetic tape. A computer program was developed to integrate the area between the pressure-volume curve and resting end-expiratory esophageal pressure for both inspiration and expiration as shown in Fig. 2. This area has the dimensions of work and corresponds reasonably well to the work done on the lung by the chest wall, diaphragm, and abdominal muscles (1–3). When the previously recorded tape was played back into the programmed computer, it calculated work for each breath and then averaged work per breath and the rate of work per minute for a 5-min period at each level of inspiratory resistance. It also calculated the product of pressure and time during active inspiration expressed as an average per minute.

Cardiac output. To assess the contribution of changes in cardiac output to the large changes in flows seen in the respiratory and control muscles during inspiratory resistance, cardiac output was measured in a separate series of five similarly anesthetized dogs subjected to the same inspiratory resistances over the same time sequence. The indocyanine-green dye dilution method was used employing a Lyons model DCCO-04 computer (Physio-Tronics, Inc., Burbank, Calif.). Measurements were performed in triplicate and averaged.

Respiratory muscle blood flow. Blood flow to each of the various respiratory muscles was measured by a radioactive microsphere technique described in detail previously (4–7). 2–3 wk before the experimental procedure an 18-gauge polyvinyl catheter was implanted under anesthesia into the left atrium through the left atrial appendage and exteriorized at the back of the neck. At the time of the experiment, blood flows to individual muscles were measured at each level of inspiratory resistance: Radioactive microspheres (25 mm in diameter and labeled with ^{125}I, ^{141}Ce, ^{85}Sr, or ^{46}Sc) were injected into the left atrium from whence they were regionally distributed in proportion to regional blood flow at the time of the injection (4,6). While microspheres of 25 mm might be inaccurate for small regional differences within an organ, they accurately reflect overall organ flow or flow to large regions (8).

To accurately measure muscle blood flow the microspheres must be completely trapped by the capillary bed. This was demonstrated for the diaphragm by withdrawing blood from the left inferior phrenic vein of two dogs during microsphere injections at resting ventilation, at the highest inspiratory resistance, and during hyperventilation induced by 7% inspired CO_2. The fraction of microspheres not trapped by the muscle's capillary bed could then be calculated by comparison of simultaneous venous and arterial reference blood samples (7). Less than 0.5% of the microspheres entering the diaphragmatic capillary bed leaked into the venous drainage under any of those conditions.

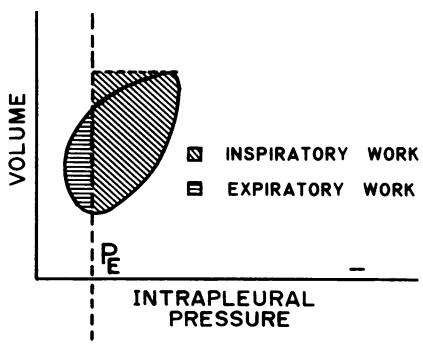

FIGURE 2 Inspiratory and expiratory work of breathing was calculated by computer integration of the areas shown.

At each level of inspiratory resistance approximately 500,000 microspheres were injected into the left atrial line and flushed in with 30 ml of warm saline over 30 s. Absolute muscle blood flow was measured by the reference sample method (7). Reference blood was withdrawn at fixed flow (10 ml/min) with a withdrawal pump (Holter, model 911, Extracorporeal Medical Specialties, Inc., King of Prussia, Pa.) from each femoral artery, beginning simultaneously with injection of the microspheres and continuing for 90 s thereafter. The use of two reference samples allowed an index of randomness of mixing of microspheres. Where radioactive counts from the two samples differed by more than 15% the data were discarded. Since the microspheres are distributed to all arteries in proportion to flow, muscle flow was determined by the equation: muscle flow (ml/g per min) = (arterial reference flow [ml/min] × muscle nuclide activity per gram/arterial reference nuclide activity). For each animal the spillover of counts between isotopes was corrected by analyzing counts for each isotope in the reference blood sample obtained during injection of each isotope label.

Buckberg et al. have shown that approximately 400 microspheres per sample are required to achieve 95% confidence that the flow estimates lie within ±10% of the true value (6). Our lowest flows per gram of muscle were approximately 0.05 ml/g per min; since cardiac outputs were approximately 3 liters/min and since we injected 500,000 microspheres each time, 50-g samples were needed to ensure 400 microspheres. Therefore, where muscle size would allow, at least 50 g was obtained to minimize statistical sampling error in blood flow calculations.

To assess the reproducibility of measurements of respiratory muscle blood flow by this technique, 14 duplicate measurements were made in a preliminary study. The mean blood flow per gram ranged from 0.01 ml/g per min to 1.87 ml/g per min. The SD of the percentage difference of duplicate measurements from the mean was 11.8±5.1%.

Respiratory muscle weights. Since accurate dissection of each respiratory muscle is prohibitively slow, an initial study was carried out on six healthy mongrel dogs with a similar weight range (17–29 kg). Each animal was sacrificed by an overdose of pentobarbital and careful quantitative dissection of the primary and accessory muscles of respiration (9) was accomplished (Table I). In preliminary studies it was found that blood flow to the central tendon of the diaphragm did not change with increasing work of breathing; thus, it was excluded from all analysis of flow to and weight of that muscle. All accessory muscles were expressed as a ratio (R = accessory muscle weight ÷ diaphragmatic weight). In each experimental animal thereafter, the diaphragm was completely excised and weighed; the total weight of any accessory muscle was estimated by multiplying the observed diaphragm weight by the R value for that muscle. Then total muscle blood flow was obtained by multiplying this accessory muscle weight by the blood flow per gram in a representative sample of that muscle.

Respiratory muscle oxygen consumption. To obtain venous blood from the diaphragm a no. 7F catheter (ASCI 5423) was advanced under fluoroscopic control from the left femoral vein into the left inferior phrenic vein as described by Rochester (10). In every animal proper positioning of the catheter was confirmed by dissection after completion of the experiment. In two animals the catheter was no longer present in the diaphragmatic vein at necropsy, so these animals were excluded from oxygen consumption calculations.

At each work rate heparinized blood samples were withdrawn simultaneously from the diaphragmatic vein and femoral artery. These were analyzed immediately for P_{O_2} (Instrumentation Laboratory, Inc., Lexington, Mass., 313 Blood Gas Analyzer), O_2 saturation (Instrumentation Laboratory, Inc., Co-oximeter), and hemoglobin (Beckman Instruments, Inc., Fullerton, Calif., DB Spectrophotometer). Arterial and venous oxygen contents were calculated and arteriovenous content difference determined for each run. Also, the oxygen and carbon dioxide content of expired gas were measured (Beckman Instruments, Inc., Oxygen Analyzer, model 242B, and Beckman Medical Gas Analyzer, model 240M, respectively). The content differences so obtained were multiplied by the expired minute volume, measured in a Tissot spirometer, to obtain total body oxygen consumption and carbon dioxide production.

Since the total respiratory muscle blood flow and diaphragmatic arteriovenous oxygen content differences (A-V Δ Co_2)[1] are known for each animal, total respiratory muscle oxygen consumption may be calculated by multiplication if it is assumed that oxygen extraction is similar for the other muscles of respiration. To assess this assumption, in three dogs a catheter was advanced under fluoroscopic control into the azygous vein as well as the left inferior phrenic vein, and oxygen contents of the venous bloods were compared at different loads.

Respiratory muscle metabolism. Arterial and diaphragmatic venous samples were taken for lactate and pyruvate analysis at each level of inspiratory resistance; samples were chilled and immediately transferred to cold 8% perchloric acid. After shaking for 30 s the tubes were centrifuged in

TABLE I
Respiratory Muscle Weights

Muscle	Average weight	R value*
	g	
Inspiratory muscles		
Diaphragm	103.6 (±6.8)	—
External intercostals	73.6 (±5.6)	0.76 (±0.04)
Scalenes	56.4 (±5.9)	0.51 (±0.03)
Serratus dorsalis	43.0 (±4.9)	0.39 (±0.01)
Serratus ventralis	219.7 (±12.5)	2.06 (±0.17)
Expiratory muscles		
Transverse abdominal	80.5 (±5.5)	0.83 (±0.05)
Internal intercostals	139.2 (±17.9)	1.41 (±0.08)
Internal oblique	65.1 (±4.4)	0.60 (±0.04)
External oblique	158.4 (±10.4)	1.48 (±0.09)
Rectus abdominis	168.4 (±15.9)	1.74 (±0.16)
Ileocostalis	42.8 (±3.9)	0.40 (±0.04)

Mean (±SEM). Average weight of dogs, 21.23±1.36 kg.
* R value = accessory muscle weight ÷ diaphragm weight.

[1] *Abbreviations used in this paper:* A-aΔP_{O_2}, alveolar-arterial gradient of oxygen tension; A-V Δ Co_2, arteriovenous oxygen content difference; PPTI, inspiratory pleural-pressure time index; $\dot{Q}_D$, flow to the diaphragm; $\dot{Q}_E$, external intercostal blood flow; $\dot{Q}_{RS}$, total blood flow to the muscles of respiration; $\dot{Q}_D/\dot{Q}_{RS}$, ratio of diaphragmatic to total respiratory muscle blood flow; $\Delta\dot{Q}_D/\Delta Q_{RS}$, ratio of increase in diaphragmatic blood flow to the increase in total respiratory muscle blood flow; $\dot{V}_A$, alveolar ventilation; $\dot{V}_{CO_2}$, CO_2 production; V_D/V_T, ratio of dead space to tidal volume ventilation; $\dot{V}_E$, expired minute volume; $\dot{V}_{O_2}$, oxygen consumption; $\dot{W}$, work of breathing.

TABLE II
Ventilation and Gas Exchange during Inspiratory Resistance

	Resistor			
	None	Low	Medium	High
Respiratory rate	18.9 (±2.6)	28.2* (±4.2)	38.1* (±6.5)	58.2* (±5.1)
Minute volume, *liters/min*	6.56 (±0.85)	8.24 (±1.08)	8.47* (±1.04)	9.98* (±1.32)
A-aΔP_{O_2}, *mm Hg*	18.2 (±3.4)	18.5 (±4.2)	24.8* (±3.8)	38.8* (±3.8)
$\dot{V}_{CO_2}$, *ml/min*	146 (±22)	164 (±26)	172* (±7)	250* (±13)
$\dot{V}_A$, *liters/min*	3.63 (±0.75)	4.17* (±0.81)	4.38* (±0.63)	5.01* (±0.52)
$\dot{V}_D/\dot{V}_T$	0.44 (±0.05)	0.49 (±0.04)	0.47 (±0.05)	0.49 (±0.04)

Mean (±SEM).
*Significantly changed from no resistance ($P < 0.05$).

the cold and the supernate frozen. Samples were analysed for lactate and pyruvate by the ultraviolet absorption method (11).

Experimental protocol. Each animal was placed in the plethysmograph and breathed spontaneously to the outside first with no added resistance and then sequentially through three graded inspiratory resistors. Resistors were constructed using large bore tubing with internal baffles so that airflow was turbulent throughout the range of flows measured. Thus, resistance was linearly related to flow (i.e., resistance = $k_r \times$ flow) with $k_r = 90$, $k_r = 300$, or $k_r = 1{,}200$ cm H_2O/(liter/s)^2 for low, medium, and high resistors, respectively. After a 15-min equilibration period at each level of resistance, the esophageal pressure and box volume changes were recorded for calculating work of breathing, radiolabeled microspheres were injected to measure respiratory muscle blood flow, and blood samples were drawn from the femoral artery and diaphragmatic vein for blood gas and lactate-pyruvate measurements.

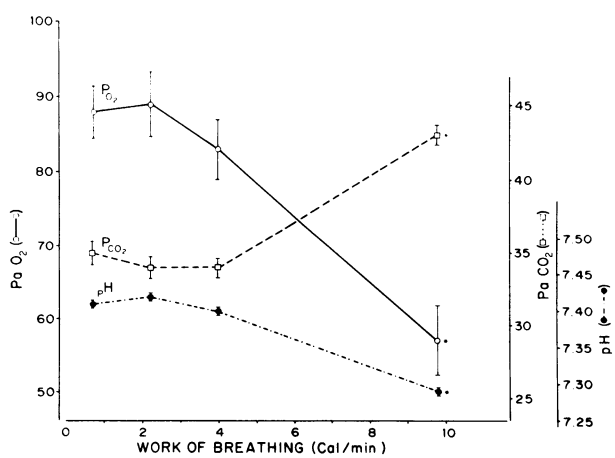

FIGURE 3 Arterial blood gas values during inspiratory resistance breathing. Mean ± SE. *Significantly changed from quiet breathing, $P < 0.02$.

TABLE III
Work of Breathing during Inspiratory Resistance

	Imposed load			
	None	Low (k_r = 90)	Medium (k_r = 300)	High (k_r = 1,200)
Work rate				
Inspiration, *Cal/min*	0.56 (±0.10)	1.95* (±0.25)	3.47* (±0.39)	9.41* (±1.34)
Expiration, *Cal/min*	0.12 (±0.07)	0.24 (±0.09)	0.47 (±0.24)	0.33 (±0.13)
Total, *Cal/min*	0.68 (±0.07)	2.19* (±0.23)	3.94* (±0.30)	9.74* (±1.34)
PPTI, *cm H_2O-s/min*	52.4 (±9.7)	177.9* (±18.8)	362.0* (±42.0)	812.5* (±90.6)

Mean (±SEM).
* Significantly changed from resting value ($P < 0.05$).

Statistics. Statistical analysis was performed with the Student's t test for paired data in all cases except where linear regressions are specified.

RESULTS

Ventilation and gas exchange. Parameters of ventilation and gas exchange are summarized in Table II and Fig. 3. Respiratory rate increased progressively ($P < 0.001$) and expired minute volume ($\dot{V}_E$) increased slightly ($P < 0.03$). At the high resistance level the arterial carbon dioxide tension rose ($P < 0.02$) as CO_2 production ($\dot{V}_{CO_2}$) increased out of proportion to the alveolar ventilation ($\dot{V}_A$); pH fell simultaneously ($P < 0.001$). The arterial oxygen tension also fell at medium ($P < 0.01$) and high ($P < 0.002$) resistances. Thus at the highest load arterial P_{CO_2} was rising in the face of an increasing chemical drive to ventilation from acidosis and hypoxemia. Thus hypoxemia was associated with an increase in the alveolar-arterial gradient of oxygen tension (A-a Δ P_{O_2}) without an increase in the ratio of dead space to tidal volume ventilation (V_D/V_T). The high V_D/V_T at rest is, at least in part, due to the added dead space of the apparatus used.

Work of breathing. Table III lists the changes in the rate of work of breathing observed during inspiratory resistance breathing. Work rate increased approximately 15-fold ($P < 0.0001$). Expiratory work rate did not contribute significantly to increases in total rate of work of breathing. The inspiratory pleural pressure-time product also increased 15-fold ($P < 0.0001$). All values remained constant over the 5-min sampling period, indicating that each animal had reached a steady rate of respiratory work and ventilation.

Cardiac output and blood pressure. The cardiac outputs in the separate series of animals exposed to the same resistances over the same time sequence

TABLE IV
Blood Flow during Inspiratory Resistance

	Resistor			
	None	Low	Medium	High
		ml/g/min		
Inspiratory muscles				
Diaphragm	0.08(±0.02)	0.18(±0.04)*	0.42(±0.04)*	2.07(±0.41)*
External intercostals	0.07(±0.03)	0.09(±0.03)	0.16(±0.02)*	0.68(±0.23)*
Scalenes	0.08(±0.02)	0.07(±0.01)	0.06(±0.01)	0.29(±0.07)*
Serratus dorsalis	0.07(±0.02)	0.06(±0.00)	0.06(±0.01)	0.12(±0.02)
Serratus ventralis	0.04(±0.00)	0.04(±0.00)	0.04(±0.01)	0.02(±0.00)
Expiratory muscles				
Transverse abdominal	0.06(±0.01)	0.05(±0.01)	0.12(±0.02)	0.23(±0.05)*
Internal intercostals	0.11(±0.03)	0.13(±0.03)	0.16(±0.04)	0.54(±0.19)*
Internal oblique	0.05(±0.00)	0.06(±0.01)	0.08(±0.03)	0.14(±0.01)
External oblique	0.03(±0.00)	0.03(±0.00)	0.04(±0.01)	0.12(±0.03)
Rectus abdominis	0.07(±0.02)	0.05(±0.02)	0.03(±0.00)	0.02(±0.01)
Ileocostalis	0.06(±0.01)	0.05(±0.00)	0.08(±0.01)	0.03(±0.01)
Controls (grouped)	0.06(±0.01)	0.05(±0.01)‡	0.05(±0.01)‡	0.04(±0.00)‡

Mean (±SEM).
* Significantly increased from rest ($P < 0.05$).
‡ Significantly decreased from rest ($P < 0.01$).

did not change significantly (no resistance, 3.08±0.42; low, 2.86±0.33; medium, 3.41±0.50; high, 3.37±0.38 liters/s). Mean aortic blood pressure also did not change significantly (none, 117±13; low, 119±13; medium, 122±7; high, 119±6 mm Hg), nor did either its systolic or diastolic components.

Respiratory muscle blood flow. The blood flow per gram for the respiratory muscles at resting ventilation and graded inspiratory resistances are shown in Table IV and Fig. 4. Flow to the diaphragm ($\dot{Q}_D$) increased exponentially with increasing rate of work of breathing ($\dot{W}$) (Fig. 5).

Diaphragmatic blood flow also increased exponentially with increasing inspiratory pleural pressure-time index (PPTI): $\sqrt{\dot{Q}_D} = 0.00144\ PPTI + 0.173$, $n = 27$, $r = 0.94$, $P < 0.0001$.

The external intercostal blood flow ($\dot{Q}_E$) also rose exponentially with the rate of work of breathing but with a much lower slope: $\sqrt{\dot{Q}_E} = 0.064\ \dot{W} + 0.150$, $n = 27$, $r = 0.86$, $P < 0.001$.

Among inspiratory muscles the only other one that augmented blood flow significantly was the scalene group, which came into play only at the highest work rate ($P < 0.01$). The serratus dorsalis flow also appeared to rise at the highest load, but this was not significant ($P = 0.18$). The serratus ventralis, often considered an accessory muscle of inspiration in dogs (9), actually had a decrease in blood flow of borderline significance ($P = 0.06$) similar to control muscles.

Several expiratory muscles had increased blood flows during increased inspiratory work: The transverse ab-

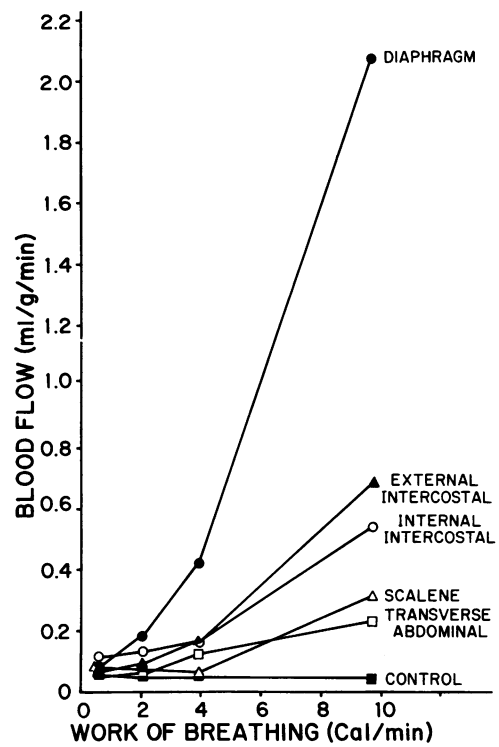

FIGURE 4 Blood flow to the various muscles of respiration during resting ventilation and graded inspiratory resistances. Flow increased significantly ($P < 0.05$) at each level of work rate for the diaphragm, at medium and high levels for the external intercostals and transverse abdominal, and only at high load for the rest. Control muscles decreased significantly at each level.

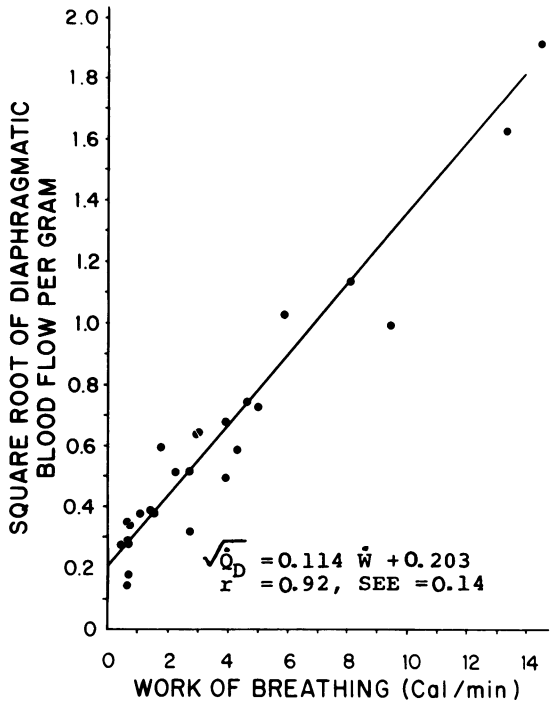

FIGURE 5 Relationship of the square root of diaphragmatic blood flow per gram to the rate of work of breathing in Cal/min showing close correlation of individual data to a straight line. Each point is a single determination in one of the seven animals. The relationship does not differ significantly from a straight line, suggesting that muscle blood flow is exponentially related to the mechanical work.

dominal blood flow rose significantly at medium ($P < 0.004$) and high ($P < 0.05$) inspiratory loads and the internal intercostal flow increased at the high work rate only ($P < 0.05$). The internal and external oblique muscles appeared to have augmented flow at the high work rate, but this was not significantly different from rest ($P = 0.17$ and $P = 0.20$, respectively). The rectus abdominis and ileocostalis muscles' blood flows decreased insignificantly similar to control muscles (pectoralis, sternohyoideus, and triceps brachii) which individually decreased insignificantly. When these control muscles were considered as a group, there was a significant fall in blood flow ($P < 0.001$).

If one assumes that the respiratory muscles under the condition of inspiratory resistance are those whose flow increases (diaphragm, intercostals, transverse abdominal, scalenes, serratus dorsalis, and obliques), then total blood flow to the muscles of respiration ($\dot{Q}_{RS}$) can be computed (Table V). The muscles of respiration under these conditions constituted 3.4% of total body weight (see Table I). At resting ventilation the total blood flow to the muscles of respiration was only 1.5% of the cardiac output, but at the highest level of resistance studied this fraction rose to 10.6%. These comparisons are, of course, only approximate as blood flows and cardiac outputs were measured in separate series of animals of similar weight. At resting ventilation the diaphragm received 17% of the total respiratory muscle blood flow ($\dot{Q}_D/\dot{Q}_{RS}$), a ratio slightly larger than the percentage the diaphragm contributes to total respiratory muscle weight (14%), probably because most of the accessory muscles of respiration were not in use during quiet breathing. As the rate of work of breathing increased due to inspiratory resistance, blood flow to the diaphragm represented a progressively increasing proportion of flow to the respiratory muscles, exceeding 50% at the highest load. At the highest load blood flow to the diaphragm constituted 5.5% of the cardiac output. Neither the total respiratory muscle blood flow nor the blood flow to any of the individual respiratory muscles seemed to have reached a plateau at the work loads imposed.

Oxygen extraction. The A-V Δ Co_2 is plotted against the rate of work of breathing in Fig. 6A and against $\dot{Q}_D$ in Fig. 6B. During inspiratory resistance the A-V Δ Co_2 increased significantly between resting ventilation and low resistance ($P < 0.04$);

TABLE V
Total Blood Flow to Various Respiratory Muscles during Inspiratory Resistance

	Resistor			
	None	Low	Medium	High
	ml/min			
Total blood flow				
Diaphragm ($\dot{Q}_D$)	7.7 (±1.5)	18.2 (±4.7)	41.2 (±6.5)	209.5 (±58.0)
External intercostals	5.1 (±1.8)	6.0 (±2.0)	11.2 (±1.1)	50.6 (±15.9)
Scalenes	4.1 (±1.1)	3.7 (±0.6)	3.3 (±0.6)	15.3 (±4.0)
Serratus dorsalis	2.9 (±0.8)	2.6 (±0.2)	2.4 (±0.5)	4.8 (±0.7)
Internal intercostals	14.0 (±4.0)	16.4 (±3.8)	21.5 (±5.5)	75.7 (±28.5)
Transverse abdominal	5.0 (±1.2)	4.6 (±1.1)	10.4 (±1.5)	21.3 (±6.2)
External oblique	4.9 (±1.1)	5.2 (±0.6)	5.5 (±1.6)	18.9 (±4.8
Internal oblique	2.8 +(±0.3)	3.2 +(±1.4)	3.6 + (±2.2)	8.7 +(±0.8)
Total respiratory muscle ($\dot{Q}_{RS}$)	46.4 (±8.3)	59.9 (±5.3)	99.0 (±10.5)	404.8 (±103.1)
$\dot{Q}_D/\dot{Q}_{RS}$	0.17 (±0.02)	0.30 (±0.04)	0.42 (±0.04)	0.52 (±0.05)
$\Delta\dot{Q}_D/\Delta\dot{Q}_{RS}$	— —	0.77 (±0.10)	0.63 (±0.05)	0.56 (±0.07)

Mean (±SEM).

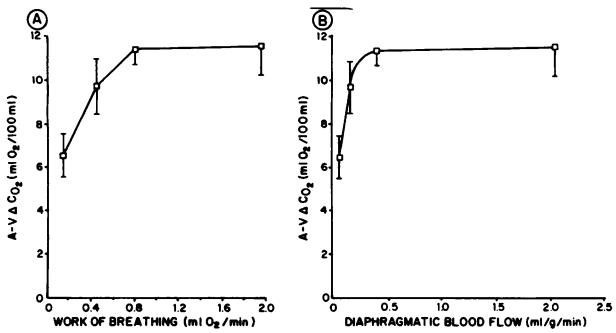

FIGURE 6 The relationship between average arterial-diaphragmatic venous oxygen content difference (A-V Δ Co_2) and the rate work of breathing (A) or diaphragmatic blood flow (B). Mean ± 1 SE.

thereafter it did not change significantly as inspiratory work rate increased ($P = 0.13$ and $P = 0.99$, respectively). As demonstrated in Fig. 6B, the response to low levels of inspiratory resistance is an increase in oxygen extraction while $\dot{Q}_D$ increases little; at greater levels of resistance, oxygen delivery is accomplished predominantly by increased blood flow.

Respiratory muscle oxygen consumption and efficiency. Total oxygen consumption of the muscles of respiration has been calculated as the product of total respiratory muscle blood flow and A-V O_2 content differences across the diaphragm (Table VI), making the assumption that oxygen extraction by the diaphragm is representative of the other respiratory muscles. The oxygen consumption ($\dot{V}_{O_2}$) increased expotentially as inspiratory load: $\sqrt{\dot{V}_{O_2}} = 2.60\ \dot{W} + 1.26$, $n = 19$, $r = 0.95$, $P < 0.0001$.

Since $\dot{W}$ and respiratory muscle $\dot{V}_{O_2}$ are in the same units (ml O_2/min), efficiency of the respiratory muscles may be calculated as $100 \times \Delta\dot{W}/\Delta\dot{V}_{O_2}$ where $\Delta\dot{W}$ and $\Delta\dot{V}_{O_2}$ are changes from resting controls (Table VI). Efficiency falls progressively from an initial value of 13.3% to a low of 4.3% at the highest resistive load. It is likely that as inspiratory resistance increases, more metabolic energy is being used to generate the tension in the muscles needed to reach the pressures required for gas flow. Thus, a smaller fraction of metabolic work is being used for shortening of muscle (mechanical work output).

We also calculated the respiratory muscle oxygen consumption from changes in total body oxygen consumption during each increment in work load (12–24) in these same animals (Table VI): The total body oxygen consumption at resting ventilation is subtracted from total body oxygen consumption at increased work of breathing, and the difference is assumed to be due to the increased oxygen consumption in respiratory muscles necessary for the increased work of breathing (difference between resting work and increased work). This estimate of respiratory muscle oxygen consumption was consistently greater than that determined by the direct blood flow-oxygen content method. Thus, the efficiency of the respiratory muscles calculated from expired oxygen concentrations was much less except at very high work loads.

Respiratory muscle metabolism. Table VII summarizes the results of lactate and pyruvate determinations during inspiratory resistance. All arterial and venous concentrations of lactate or pyruvate were within normal limits (11,25–30) and did not change significantly with increasing rate of work of breathing ($P < 0.20$) except for a slight rise on the highest resistor which did not quite reach statistical significance ($P = 0.12$). The gradients of lactate and pyruvate across the diaphragm did not change significantly nor did the arterial or venous lactate/pyruvate ratios ($P > 0.30$). When arterial and venous lactate values were corrected for simultaneous pyruvate samples by the method of Huckabee (27) the gradient for "excess lactate" across the diaphragm ("excess lactate" = Δ lactate − Δ pyruvate × control lactate/control pyruvate) was consistently a small negative value and did not change significantly with increasing resistance.

DISCUSSION

Ventilation and gas exchange. The results in Table II suggest that the lung was failing as a gas exchange organ in our animals during high inspiratory resistance loads. Two possible explanations seem likely: either the animals developed pulmonary edema associated

TABLE VI
Efficiency of the Respiratory Muscles

	Resistance			
	None	Low	Medium	High
$\dot{Q}_{RS}$ × A-V Δ Co_2 method (n = 5)				
$\dot{V}_{O_2}$, *ml O_2/min*	3.5 (±0.4)	6.0 (±0.8)	11.8 (±2.2)	45.2 (±13.1)
$\Delta\dot{V}_{O_2}$, *ml O_2/min*	— —	2.5 (±0.4)	8.3 (±2.4)	41.2 (±13.2)
$\Delta\dot{W}$, *ml O_2/min*	— —	0.33 (±0.04)	0.71 (±0.04)	1.81 (±0.31)
Efficiency, %	— —	13.3 (±2.9)	8.8 (±2.8)	4.3 (±0.9)
Total Body $\dot{V}_{O_2}$ method (n = 5)				
$\dot{V}_{O_2}$, *ml O_2/min*	156 (±25)	193 (±32)	183 (±23)	199 (±22)
$\Delta\dot{V}_{O_2}$, *ml O_2/min*	— —	36 (±15)	26 (±7)	45 (±21)
Efficiency, %	— —	0.8 (±0.3)	2.5 (±0.1)	4.0 (±1.1)

Mean (±SEM).

TABLE VII
Diaphragm Lactate-Pyruvate Metabolism during Inspiratory Resistance

	Resistor			
	None	Low	Medium	High
	mg/100 ml			
Arterial lactate	5.00 (±0.26)	5.17 (±0.55)	5.03 (±0.59)	6.70 (±0.75)
Venous lactate	6.02 (±0.44)	5.38 (±0.38)	5.57 (±0.61)	7.33 (±1.32)
V-A lactate	1.02 (±0.40)	0.21 (±0.29)	0.54 (±0.70)	0.63 (±0.68)
Arterial pyruvate	0.68 (±0.07)	0.59 (±0.10)	0.54 (±0.08)	0.76 (±0.16)
Venous pyruvate	0.68 (±0.11)	0.59 (±0.08)	0.52 (±0.09)	0.64 (±0.17)
V-A pyruvate	0.00 (±0.10)	0.00 (±0.06)	−0.02 (±0.13)	−0.12 (±0.08)
V-A excess lactate	— —	−0.92 (±0.72)	−0.59 (±0.86)	−1.29 (±1.38)

Mean (±SEM).

with the central shift in blood volume induced by the negative intrathoracic pressures caused by high resistances to inspiration, or the animals might have moved to lower than normal lung volumes because of impeded inspiration and free expiration, with resultant atelectasis and shunts. There was no evidence of pulmonary edema grossly at necropsy. Low lung volumes were suspected during the studies, but were not confirmed by objective measurements. It is clear from the tracings that, although alveolar ventilation was maintained, on the higher resistances the animals lost the ability to sigh periodically and breathed with rapid respiratory rates and smaller tidal volumes. Both of these effects would predispose the animal to progressive atelectasis.

Respiratory muscle blood flow. Blood flow to the diaphragm increased much more than flow to any other inspiratory muscle during increasing work of breathing due to inspiratory resistance (Fig. 3 and Table III). Blood flow was augmented to several expiratory muscles during inspiratory resistance breathing even though expiratory pressure volume work on the lung did not increase significantly. Since the stimulus for increased blood flow is almost certainly increased muscle work rate (28–30) the augmented flows were unexpected. One explanation might be that the expiratory muscles were acting during expiration to move the diaphragm and rib cages to a position where they have better mechanical advantage in the subsequent inspiration (31).

While these respiratory muscles had increased blood flow, nonrespiratory control muscles showed a decrease in flow. This finding is evidence for redistribution to the muscles being used for ventilatory work and away from the rest of the body musculature. Furthermore, since cardiac output and blood pressure were unchanged, there was an increase in resistance in nonutilized muscles as well as a fall in resistance in the vascular bed of the exercising muscle.

To our knowledge there are no previous reports of the distribution of blood flow among respiratory muscles, but there are a few studies which have measured diaphragmatic blood flow alone: Rochester and Pradel-Guena, with clearance of ^{133}xenon injected into the diaphragm of dogs (32), reported a flow during resting ventilation of 0.42 ml/g per min. Mognoni et al., with the technique ^{86}Rb uptake by the muscles (33), obtained a diaphragmatic flow during quiet breathing of 0.40 ml/g per min. Both of these methods require assumptions about diffusability of the isotope and appear to have overestimated flow. Subsequently Rochester, with the Kety-Schmidt technique (10) revised the estimate of diaphragmatic flow during resting ventilation to 0.20 ml/g per min, still somewhat greater than our estimate of 0.08 ml/g per min. More recently Rochester and Bettini have observed that diaphragmatic flow increased linearly with increasing rate of work of breathing as assessed by a pleural pressure-time index from values ranging from 0.10 to 0.36 ml/g per min at rest to values ranging from 0.14 to 0.59 ml/g per min on CO_2 inhalation and various resistors (34). In our animals the relationship between the PPTI and diaphragmatic blood flow was exponential. Over a similar range of blood flows to those of Rochester and Betini our data might also have appeared linear, the exponential nature of the curve becoming more apparent at higher diaphragmatic blood flows and higher work loads. Hales, with a microsphere technique similar to ours observed a diaphragmatic flow at resting ventilation in sheep of 0.17 ml/g per min (35). Their awake, nontracheostomized animals likely had greater minute volumes at rest (36) than the anesthetized animals in Rochester's and our studies. Flows at rest to control muscles (0.03–0.09 ml/g per min) were quite similar to the values we obtained (0.06 ml/g per min). With the increased ventilatory efforts induced by panting in response to heat stress, blood flow increased to 2.09 ml/g per min to the crus and 1.72 ml/g per min in the rest of the diaphragmatic muscle, values similar to the high flows obtained by us on the highest resistance. He also measured blood flow to the intercostal muscles at rest and panting. Flow at rest was 0.08 ml/g per min and during

panting was 0.29 ml/g per min. However, the internal and external intercostals were not separated and neither minute volume nor work of respiration were measured, so direct comparison with our results is precluded.

Since our highest values of diaphragmatic blood flow during inspiratory resistance are much higher than those observed by Rochester and Bettini also during inspiratory resistance (34), but are similar to Hales' results during panting induced by heat stress (35), it seemed possible that our animals might have differed from Rochester and Bettini's by being exposed to a heat stress inside the body plethysmograph. However, the temperature inside the flow plethysmograph never exceeded 2°C above room temperature and rectal temperature when monitored in a single animal rose only 1°C during the complete study. This degree of rise in rectal temperature is consistent with exercise in a normal environment (37) and does not suggest externally applied heat stress. Thus, heat stress does not seem a likely explanation of the difference between the two studies in maximal blood flow to the diaphragm. Rather, it likely is a function of the higher work loads reached in our animals and perhaps of the difference in method of measuring flow.

It has been demonstrated for skeletal muscle that the change in blood flow from rest to exercise correlates with the increased work rate performed by that muscle (28–30). If it is assumed that the same is true for respiratory muscles, the fractional contribution of each muscle to the increased work rate of all respiratory muscles during inspiratory resistance should be similar to the fractional increase in blood flow. The last line in Table V indicates that the fractional increase in blood flow to the diaphragm ($\Delta\dot{Q}_D/\Delta\dot{Q}_{RS}$) is very high (0.77) at low resistive loads. This fractional contribution of the diaphragm falls slightly at greater resistances as the accessory muscles come into play but is still greater than 50% at very high resistances. Thus, it appears that the diaphragm produces the majority of the power output required to overcome inspiratory resistance, just as it performs the majority of resting ventilation in the supine position (38–41). This large fractional contribution of the diaphragm to inspiratory resistance work is disproportionate to its weight fraction (0.14), further supporting the concept of preferential use of the diaphragm in supine animals during tidal volume breathing, either with or without increased resistance. Hales' results in panting sheep referred to above which showed much greater increases in blood flow to the diaphragm than to the intercostals suggest that the diaphragm is also preferentially used during panting (35).

There was a relatively large standard error of measurements of flow per gram to respiratory muscles in our animals both at resting ventilation where flows were low and when flows increased due to resistance breathing. Similarly large variability was observed by Hales (35) when he measured diaphragm and intercostal blood flows in sheep at rest (SE = ±21% of mean) and panting (±16%). In part this is due to the variability inherent in using the microsphere technique to measure flows to organs receiving less than 1% of the cardiac output (42, 43). Also, Rochester (10) has shown that blood flow to the diaphragm is a function of cardiac output and A-V Δ CO_2, both of which showed significant variability among animals in this study. Finally, as the equations above and Fig. 5 show, blood flow to the individual muscles is directly related to the rate of work of breathing; and there was a significant variability in the rate of work of breathing among animals at each resistance load (see Table III).

TABLE VIII
Venous Oxygen Contents

	Resistor			
	None	Low	Medium	High
	ml O_2/100 ml			
Diaphragm	4.25 (±1.98)	2.55 (±1.23)	0.96 (±0.35)	1.16 (±0.16)
Azygous	8.83 (±2.56)	5.89 (±2.50)	2.83 (±1.16)	1.30 (±0.20)

Mean (±SEM).

Respiratory muscle oxygen consumption. Our method assumes that oxygen extraction by the other muscles of respiration are similar to that of the diaphragm. Azygous vein oxygen contents started higher but fell to similarly low values as in blood from the diaphragm at high resistance loads (Table VIII). Since the azygous system drains other structures in addition to the intercostal muscles, this finding is consistent with the intercostals and the diaphragm having a similar arteriovenous oxygen content difference. As blood flow increased to the intercostals with increasing inspiratory resistance and remained fixed or decreased to other structures drained by the azygous system, azygous oxygen content reflected the increasing fractional contribution of intercostal venous blood. Alternatively, the intercostals might be overperfused with respect to work output at low work loads. If true, this would mean that the diaphragm is providing an even greater fraction of the total energy than we have estimated; and that, if anything, total respiratory muscle oxygen consumption was less and respiratory muscle efficiency greater than we have estimated at lower work loads.

Respiratory muscle efficiency. Previous estimates of respiratory muscle efficiency have all utilized the change in total body oxygen consumption method. Our results in dogs (Table VI) suggest that there is

a significant difference in the oxygen consumption calculated in this manner from that obtained by direct determination of blood flow × oxygen extraction, so that except at the highest work load the former method gives higher values for oxygen consumption. Thus, efficiency calculated from expired gas analysis was much less except at very high work loads (Table VI). Previous estimates of respiratory muscle efficiency utilizing expired gas analysis under conditions of inspiratory resistance have reported values lower than the 13.3% we obtained using our lowest resistance which is of similar magnitude to that usable in awake subjects. When mechanical work rate was assessed by the minute volume × the pressure drop across an external water seal, Cain and Otis found an efficiency of 3% (14); Campbell et al., around 9% (17, 20); Cherniack, an average of 8.6% (19). McGregor and Becklake (1), with an esophageal pressure-expired volume method similar to ours to assess mechanical work rate found an efficiency during resistance of only 1%. These estimates are similar to the 1–4% efficiency we obtained by the expired gas method. We conclude that total body oxygen consumption changes underestimate the efficiency of respiratory muscles. This same conclusion was reached by Hales during studies of respiratory muscle blood flow in sheep caused to pant by heat stress (35). Perhaps the stressful conditions of the procedure increased oxygen consumption elsewhere in the body due to epinephrine release, posture maintenance during increased ventilatory efforts, altered acid-base balance, or other unappreciated factors.

On the other hand our estimates of efficiency of respiratory muscles are lower than that measured for other skeletal muscles (i.e. 19–25%) (44). A partial explanation mentioned earlier may be that during resistance breathing there is a component of isometric work necessary to generate tension in the muscle, which is not measured as work output. Another source of discrepancy may be that the esophageal pressure-thoracic gas volume change method of assessing mechanical work output measures work done on the lung and does not include flow resistive or elastic work done on tissues of the thorax and abdomen which has been estimated to be as high as 28–36% of respiratory muscle work (2). Finally, this method also does not measure the "negative work" done by the inspiratory muscles which show graded relaxation during expiration.

Muscle metabolism. Carlson and Pernow have demonstrated for skeletal muscle of the leg that light and moderate levels of exercise are associated with small increases in venoarterial lactate differences similar to the gradients seen in this study. As the maximal work load was approached, the lactate gradient increased sharply due to anaerobic metabolism of the exercising muscle (45). However, lactate and pyruvate are in equilibrium and rises in pyruvate will cause increases in lactate not associated with tissue hypoxia and acidosis (27). When pyruvate samples were obtained and lactate concentrations corrected for simultaneous pyruvate by the method of Huckabee (27), they showed that this sharp rise was associated with a sharp rise in the venoarterial gradient of "excess lactate," an even better index of anaerobic metabolism (46). This suggests that oxygen delivery is a limiting factor in leg muscle exercise.

In our animals there was no increase in the venoarterial gradient of lactate or pyruvate across the diaphragm at any level of increased muscular work rate induced even by the highest inspiratory resistance (Table VII). There was also no increase in lactate out of proportion to pyruvate, as the venoarterial gradient of "excess lactate" was consistently a negative value. We conclude that the respiratory muscles were not shifting to anaerobic metabolism at any resistance load.

Conversely, Eldridge found that arterial lactate was unchanged with 15% oxygen breathing (Pa_{O_2} = 70 mm Hg) or with a seven-fold increase in respiratory work induced by dead space and inspiratory resistance; but, when these stimuli were combined, there was a significant rise in arterial lactate and fall in arterial pyruvate, so that an increased lactate/pyruvate ratio was present, indirectly suggesting anaerobic metabolism of the respiratory muscles (47). In our animals a significant arterial hypoxemia (Pa_{O_2} = 57 mm Hg) and a 16-fold increase in the rate of work of breathing due to inspiratory resistance were not accompanied by an increase in arterial lactate/pyruvate ratio. Since we could not demonstrate anaerobic metabolism in the diaphragm by directly measured gradients of lactate, pyruvate, or "excess lactate", it seems unlikely that the respiratory muscles are the source of the increased arterial lactate levels under these conditions. Rather, it is probably due to the general hypoxemia and respiratory acidosis, as the small increase in arterial and venous lactates and pyruvates seen on the highest resistance level in this study (Table VII) are similar to those seen during modest hypoxemia induced by the breathing of 15 and 13% oxygen mixture (48), or when hypoxemia exists in patients with obstructive lung disease (49). Also consistent with this assumption is Hollanders' finding in perfused rat diaphragms that increased lactate production was achieved only under conditions of tetanic stimulation, lesser tension generating stimuli being insufficient (50).

Respiratory failure. At the highest level of resistance the animals had a significant fall in arterial oxygen tension (mean Pa_{O_2} = 57 mm Hg), acidosis occurred (mean pH_a = 7.29), and carbon dioxide tension increased in every animal (mean Pa_{CO_2} = 43 mm Hg, up from a base-line mean of 34 mm Hg). Most

of the acidosis could be explained by the rise in Pa_{CO_2} as arterial bicarbonate was unchanged, 19.5–20. Therefore, in this model at the highest work load significant arterial hypoxemia developed in part as a consequence of disturbed ventilation-perfusion relationships and in part as a consequence of early CO_2 retention. Respiratory acidosis with a component of metabolic acidosis developed at the highest work load. Thus, at the highest work load CO_2 retention was occuring in the face of increasing chemical drive to respiration from both acidosis and arterial hypoxemia. Early respiratory failure was occuring before there was evidence for impaired oxygen delivery to muscles of breathing as might be reflected by reaching a plateau for blood flow or oxygen consumption or by excess lactate production by the diaphragm.

Thus there must be another etiology of respiratory failure under conditions of inspiratory resistance. The muscles may have failed for some reason other than oxygen delivery: there may have been insufficient substrate available to convert into metabolic energy. For example, glycogen depletion has been shown to limit exercise capacity of peripheral skeletal muscle (51). While it seems unlikely that this would have occurred in the relatively short duration of this experiment, it is a possibility. Also, there may be a mechanical limit to the ability of the muscles to increase their rate of shortening while generating more tension (52). Or finally, there may have been an increase in P_{CO_2} due to the response pattern of central control mechanisms such that the muscles were not driven to fatigue at all. Neural output to the respiratory muscles may not progressively rise to prevent CO_2 retention with external loads (53) and this tendency may be aggravated by anesthesia (54). The present study cannot differentiate among these possibilities, but it does demonstrate that during inspiratory resistance oxygen delivery to the muscles is not the limiting factor.

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