Pulmonary emphysema impairs lung and respiratory muscle function leading to restricted physical capacity and accelerated morbidity and mortality consequent to respiratory muscle failure. In the absence of direct evidence, an O\textsubscript{2} supply–demand imbalance within the diaphragm and other respiratory muscles in emphysema has been considered the most likely explanation for this failure. To test this hypothesis, we utilized phosphorescence quenching techniques to measure mean microvascular P\textsubscript{O\textsubscript{2}} (P\textsubscript{O\textsubscript{2}}m) within the medial costal diaphragm of control (C, n = 10) and emphysematous (E, elastase instilled, n = 7) hamsters. P\textsubscript{O\textsubscript{2}}m and mean arterial pressure (MAP) were measured in the spontaneously breathing anesthetized hamster at inspired O\textsubscript{2} percentages of 10, 21, and 100, and across a range of mean MAPs from 40 to 115 mm Hg. At each inspired O\textsubscript{2}, diaphragm P\textsubscript{O\textsubscript{2}}m was significantly (p < 0.05) lower in E animals (10%: C, 19 ± 3; E, 9 ± 2; 21%: C, 32 ± 2; E, 21 ± 2; 100%: C, 60 ± 8; E, 36 ± 9 mm Hg). At 21% inspired O\textsubscript{2}, the P\textsubscript{O\textsubscript{2}}m decrease was correlated with reduced MAP in both C (r = 0.968) and E (r = 0.976) animals. We conclude that diaphragmatic P\textsubscript{O\textsubscript{2}}m (and therefore microvascular O\textsubscript{2} content) is decreased in emphysematous hamsters reflecting a greater diaphragmatic O\textsubscript{2} utilization at rest and a lower O\textsubscript{2} extraction reserve. According to Fick’s law, this lower P\textsubscript{O\textsubscript{2}}m will mandate an exaggerated fall in intramyocyte P\textsubscript{O\textsubscript{2}}, which is expected to accelerate muscle glycogen depletion and consequently fatigue. This provides empirical evidence in support of one possible mechanism for respiratory muscle failure in emphysema.

Chronic lung hyperinflation that is pathognomonic for pulmonary emphysema displaces the diaphragm caudally to a mechanically disadvantaged position. This condition elevates the metabolic demands placed upon the diaphragm and other respiratory muscles (1) and is associated with respiratory muscle fatigue and ultimately failure (2, 3).

In the widely accepted hamster model of emphysema, the diaphragm undergoes structural and functional adaptations which include chronic shortening consequent to loss of sarcromeres in series (4–6); possible diaphragm myocyte hypertrophy (6–9) but not in all instances (5, 10); capillary neogenesis and elevated capillary tortuosity (6, 8, 9); in certain instances, mitochondrial enzymes are elevated (increased [5, 8, 11]; unchanged [11, 12]); and elevated diaphragm blood flow during exercise but not at rest (11).

For diaphragm function to be sustained, sufficient substrate flux is requisite. The most logical and enduring mechanistic basis invoked to explain respiratory muscle fatigue and failure involves an O\textsubscript{2} supply–demand imbalance. It is therefore crucial to understand more about the relationship between diaphragm O\textsubscript{2} delivery (Q\textsubscript{O\textsubscript{2}}) and O\textsubscript{2} utilization (V\textsubscript{O\textsubscript{2}}) in emphysema. It is certainly surprising that given the expected elevation of diaphragm metabolic demands (which are sufficiently powerful to cause profound diaphragmatic adaptations), diaphragm blood flow (and Q\textsubscript{O\textsubscript{2}}) is not elevated at rest (11). Under these circumstances, it would be expected that fractional O\textsubscript{2} extraction must be elevated. However, our understanding of O\textsubscript{2} exchange within the diaphragm is hampered by the complexity of the diaphragmatic blood supply and its structural and functional heterogeneity.

We have demonstrated previously that phosphorescence quenching provides a tenable method for monitoring microvascular O\textsubscript{2} pressure (P\textsubscript{O\textsubscript{2}}m) within the rodent diaphragm (13). P\textsubscript{O\textsubscript{2}}m reflects the dynamic balance between Q\textsubscript{O\textsubscript{2}} and O\textsubscript{2} removal or V\textsubscript{O\textsubscript{2}} within the microvascular space. The purpose of the present investigation was to utilize this technique to test the hypothesis that diaphragm P\textsubscript{O\textsubscript{2}}m is decreased in emphysema. Specifically, measurements of diaphragm P\textsubscript{O\textsubscript{2}}m were made across a range of inspired O\textsubscript{2} concentrations and blood pressures (hypovolemia induced by blood withdrawal) in control and emphysematous hamsters. Under each condition, P\textsubscript{O\textsubscript{2}}m was reduced systematically in the diaphragm of emphysematous hamsters.

**METHODS**

**Experimental Animals**

All procedures were conducted in accordance with the rules and regulations of the IACUC at Kansas State University. Male Syrian golden hamsters (Sasco, Omaha, NE), initially weighing ~ 120 g, were used in these studies. All animals were housed in individual cages (8 × 10 × 10 in.) and allowed free access to water and rodent chow.

**Induction of Emphysema**

Hamsters were assigned randomly to either a control (C) or emphysema (E) group and E was produced by intratracheal instillation of elastase (4–7, 14–16). Experiments were conducted 20–28 wk after elastase treatment to allow adequate time for adaptation within the diaphragm.

**Experimental Preparation**

Hamsters were anesthetized with pentobarbital sodium (40 mg/kg intraperitoneally, to effect) and the right carotid artery was cannulated. Body temperature was maintained at 37–38°C and the diaphragm was accessed via laparotomy and superfused with a warmed (38°C) Krebs–Henseleit bicarbonate-buffered solution equilibrated with 95% N\textsubscript{2}/5% CO\textsubscript{2} (22). During all experiments, the animals breathed spontaneously. Mean arterial pressure (MAP) was measured using a DigiMed blood pressure monitor (Micro-Med, Louisville, KY) and blood gases and pH using a NOVA Stat Profile (F103, Waltham, MA).

**Experimental Protocol and Conditions**

Two protocols were followed in each group of animals in the following order: (1) Using a purpose-built nosecone a series of six switches among 21, 10, and 100% inspired O\textsubscript{2} (balanced order) was performed. The inspired gas was switched rapidly < 1 s, and the new inspirate was sustained for 2–3 min at which time P\textsubscript{O\textsubscript{2}}m had stabilized. Blood samples were taken at the respective inspired O\textsubscript{2} at the end of the protocol. (2) While breathing room air (21% O\textsubscript{2}), MAP was lowered and...
Phosphorescence Quenching

Theory. The oxygen dependence of phosphorescence is described by the Stern–Volmer equation (17):

\[ T_0 / T = 1 + k_Q \times T_0 \times P_{O_2,m} \]

where \( T_0 \) and \( T \) are the phosphorescence lifetimes in the absence of oxygen and at an oxygen pressure \( P_{O_2,m} \). The quenching constant \( k_Q \) is a second-order rate constant related to the frequency of collisions between \( O_2 \) and the excited triplet state of the porphyrin and the probability of energy transfer when collisions occur. \( P_{O_2,m} \) is calculated as

\[ P_{O_2,m} \text{[mm Hg]} = \left( \frac{T_0}{T} - 1 \right) k_Q T_0 \times T_0^{-1}. \]

where \( T_0 \) and \( T \) are expressed in \( \mu s \) and \( k_Q \) in \( \text{mm Hg}^{-1} \text{s}^{-1} \). At 38°C and pH 7.4, \( k_Q = 409 \) and \( T_0 = 601 \) (18).

Phosphorescence quenching measurement of diaphragm \( P_{O_2,m} \). Of the phosphorescent probe, palladium-meso-tetra[4-carboxyphenyl]porphyrin dendrimer (R2), 15–20 mg/kg was infused via the arterial cannula. Oxyphor R2 binds tightly to albumin as evidenced by the demonstration that R2 is essentially completely bound to albumin in solution at a concentration of 0.5% albumin (19). The concentration of albumin in rat serum is \( 3 \text{ g/dl} \) (i.e., 6-fold that necessary for complete binding [20]). In addition, R2 at a pH of 7.4 possesses a net negative charge of approximately \( 14 \text{ mV} \). Both of these properties help to restrict R2 to the intravascular compartment. Diaphragm microvascular \( P_{O_2} \) (\( P_{O_2,m} \)) was determined using a PMOD 1000 Frequency Domain Phosphorimeter (Oxygen Enterprises, Ltd., Philadelphia, PA) with the common end of the bifurcated light guide placed \( 2–4 \text{ mm} \) caudal to the abdominal aspect of the medial costal region of the diaphragm about two-thirds of the radial distance between the central tendon and the costal margin (Figure 1). The excitation light (524 nm) is focused on an \( 2–3 \text{ mm} \)-diameter circle from a distance of \( 2–4 \text{ mm} \) above the muscle surface and samples blood within the microvasculature up to 500 \( \mu \text{m} \) deep. The value of \( P_{O_2,m} \) reflects principally that of capillary blood as this compartment constitutes the majority of intramuscular blood volume (21). The phosphorescence signal (700 nm) was averaged for a 200-ms interval for each \( P_{O_2,m} \) measurement and the measurements were repeated at 2-s intervals. Within biological systems, the phosphorescent probe R2 is specific for \( O_2 \) and over the range of \( P_{O_2} \) found in the muscle microcirculation can resolve \( P_{O_2} \) within \( <1 \text{ mm Hg} \).

Verification of Emphysema State

Immediately following euthanasia, lung volume was determined by saline displacement during complete immersion (15).

Statistical Analysis

Data are presented as mean ± SE. Two-way repeated measures ANOVA, one-way repeated measures ANOVA, and one-way ANOVA were used as appropriate. When differences were detected, a Student Newman–Keuls post hoc test was used to identify differences within groups and the Bonferroni post hoc test differences between groups. Comparisons between C and E groups were made by Student’s \( t \) test. Significance was accepted at \( p < 0.05 \) except in those instances where directional a priori hypotheses were established and a \( p < 0.1 \) was used.

RESULTS

Data are presented for a total of 10 C (body weight, 135 ± 12 g) and 7 E (body weight, 127 ± 3 g, \( p > 0.05 \)) animals. As expected, lung displacement weight was significantly higher in E than C animals (C, 1.4 ± 0.1; E, 2.9 ± 0.4 g, \( p < 0.05 \)) and \( P_{A \text{O}_2} \) breathing room air (21% \( O_2 \)) lower in E than C animals (Table 1, C, 90 ± 8; E, 48 ± 7 mm Hg, \( p < 0.05 \)).

Effects of Altered Inspired \( O_2 \)

Arterial blood gas, acid–base, and cardiorespiratory responses. At each inspired \( O_2 \), \( P_{A \text{O}_2} \) was reduced significantly in E com-

![Figure 1. Schematic illustrating essential features of the preparation designed to measure diaphragm microvascular \( P_{O_2}(P_{O_2,m}) \) in the hamster.](image-url)
parallel with C animals (Table 1). In C only, PaO2 was decreased at 10% O2 and increased at 100% O2 compared with the 21% O2 condition. This altered PaO2 in C elevated pH at 10% O2 and decreased pH at 100% O2 (both p < 0.05). The responses to altered inspired O2 in E hamsters were extremely variable. Breathing frequency (fB) increased with decreasing inspired O2 and decreased with 100% O2 in both C and E hamsters (all p < 0.05, Table 2). Hypoxia (10% O2) reduced heart rate in E, but not C animals compared with 21% O2 values (p < 0.05). MAP fell significantly in hypoxia compared with normoxic and hyperoxic values for both C and E hamsters but was not different between C and E animals at any inspired O2. However, in C hamsters 100% O2 increased MAP above 21% O2 values (p < 0.05).

Diaphragm P02m. At each inspired O2, diaphragm P02m was reduced significantly in E compared with C animals (Figure 2). However, the variability of this response was markedly greater under the 100% O2 condition. Figure 3 demonstrates that diaphragm P02m was decreased in E animals independent of MAP alterations secondary to the inspired gas composition.

Effects of Reduced MAP in Normoxia

Breathing normoxia, diaphragm P02m fell systematically with decreased MAP for C and E hamsters (Figure 4). Although there was considerable variability of diaphragm P02m for both E and C animals at any given MAP, diaphragm P02m was consistently lower in E than C animals. From the linear regression analysis, the diaphragm P02m difference between C and E was manifested in large part as a reduced intercept with relatively little difference in slope observed (Figure 4).

DISCUSSION

The present investigation has, for the first time, demonstrated that microvascular P02 (P02m) is lowered systematically in the diaphragm of emphysematous hamsters. This effect is present in normoxia, hypoxia, and hyperoxia and occurs across a broad range of arterial pressures that encompasses severe hypotension. Although it is intuitively obvious that arterial hypoxia consequent to emphysema should lower diaphragm P02m, the calculated microvascular O2 content in the diaphragm of emphysematous hamsters falls 2-fold more than arterial O2 content in these animals (Figure 5). In the presence of an unchanged blood flow in the diaphragm of emphysematous compared with control hamsters at rest (11), this finding supports the contention that emphysema elevates diaphragmatic energy requirements (1) without an appropriate increase in O2 delivery. The consequences of an emphysema-induced reduction of diaphragm P02m include a reduced O2 extraction reserve that will mandate a greater blood flow increase to support elevated ventilatory and thus respiratory muscle demands (e.g., physical activity), and an exacerbated fall in intramyocyte PO2 and associated metabolic sequelae (i.e., reduced [PcO2]; elevated [ADP] [23]) that are expected to enhance glycolytic activity and thereby predispose the diaphragm in emphysematous animals to fatigue.

Preparation Characteristics

It has been shown previously that the laparotomized preparation utilized herein does not perturb substantially the cardiovascular or respiratory condition of rats (13). The present data

**TABLE 1. ARTERIAL BLOOD GAS AND ACID–BASE RESPONSES TO ALTERED INSPIRED O2**

<table>
<thead>
<tr>
<th>Inspired O2%</th>
<th>10</th>
<th>21</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO2 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>30 ± 3†</td>
<td>48 ± 7†</td>
<td>142 ± 54†</td>
</tr>
<tr>
<td>E</td>
<td>29 ± 2†</td>
<td>41 ± 3</td>
<td>60 ± 4†</td>
</tr>
<tr>
<td>PaO2 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>50 ± 5†</td>
<td>90 ± 8</td>
<td>389 ± 27†</td>
</tr>
<tr>
<td>E</td>
<td>53 ± 16</td>
<td>54 ± 11</td>
<td>68 ± 8</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>7.43 ± 0.05†</td>
<td>7.28 ± 0.06</td>
<td>7.24 ± 0.05†</td>
</tr>
<tr>
<td>E</td>
<td>7.33 ± 0.11</td>
<td>7.27 ± 0.09</td>
<td>7.23 ± 0.08</td>
</tr>
</tbody>
</table>

* Definition of abbreviations: C = control; E = emphysematous; PaO2 = arterial P02; PaCO2 = arterial P02; fB = breathing frequency; HR = heart rate; MAP = mean arterial pressure.
† Data are mean ± SE.
‡ Significantly different from 21% condition.

**TABLE 2. BREATHING FREQUENCY AND CARDIOVASCULAR RESPONSES TO ALTERED INSPIRED O2**

<table>
<thead>
<tr>
<th>Inspired O2%</th>
<th>10</th>
<th>21</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>fB, breaths/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>81 ± 7†</td>
<td>71 ± 5</td>
<td>59 ± 5†</td>
</tr>
<tr>
<td>E</td>
<td>70 ± 7†</td>
<td>65 ± 4</td>
<td>57 ± 4†</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>364 ± 13</td>
<td>371 ± 12</td>
<td>376 ± 18</td>
</tr>
<tr>
<td>E</td>
<td>284 ± 38†</td>
<td>347 ± 32</td>
<td>308 ± 46</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>59 ± 4†</td>
<td>95 ± 5</td>
<td>110 ± 7†</td>
</tr>
<tr>
<td>E</td>
<td>51 ± 6†</td>
<td>95 ± 5</td>
<td>99 ± 7</td>
</tr>
</tbody>
</table>

* Data are mean ± SE.
† Significantly different from 21% condition.
demonstrate that this is true also for the hamster preparation. Specifically, comparison with the data of Sexton and Poole (11) indicate that MAP, HR, PaO2, and PaCO2 are not altered by either the anesthesia or the open abdomen condition. It should be noted, however, that the arterial pH was somewhat lower (i.e., 7.28 [present data] versus 7.36 [11]) following surgery.

The hamster is adapted to a semifossorial environment (i.e., low inspired O2, high CO2) and consequently demonstrates certain structural and functional characteristics that differ from those of other small rodents and larger mammals. Relevant to the present investigation are increased hemoglobin–O2 affinity compared with animals of similar size (i.e., P50, hamster = 28, rat = 43 mm Hg, [24, 25]), and lower sensitivity to arterial blood gas perturbations (26). Thus, control hamsters at rest elicit mild hypoxemia as seen in the present and previous investigations (11, 26–28).

Severity of the Emphysema Condition

Elastase-induced emphysema in the hamster is considered to represent a close analog for human panacinar emphysema (8, 14, 16). With this model, the pathological increase in lung compliance peaks between 2 and 12 wk postelastase instillation (16) with all lung volumes augmented within 4 to 6 mo (4, 8, 14). Crucial to the present investigation, both structural and functional diaphragmatic adaptations are manifested within this period (4, 5, 8, 11, 14, 15). The reduced PaO2 and increased lung volume (saline displacement weight) compare closely with literature values for elastase-induced emphysema in the hamster and are consistent with moderate-to-severe emphysema (11, 19, 27). Although no formal morphometric measurements of the diaphragm were made in this investigation, the costal region appeared to be thicker and the muscle fiber(s) length from central tendon to costal margin was reduced. This is consistent with previous reports from our laboratory (6) and the work of others (4, 8, 11) in the hamster model of emphysema.

Responses to Hypoxia and Hyperoxia

Control, C. Hypoxia elevated fb from 71 to 81 breaths/min, on average which reduced PaCO2 by 12 mm Hg (Tables 1 and 2). This response is mediated via peripheral chemoreceptor hypoxic sensitivity (29) and also the hypoxia-induced hypotension that is likely to potentiate the ventilatory response (30–32). Hyperoxia abolishes peripheral chemosensitivity (29), which acted to slow fb and induced hypercapnia in the hamster (Table 1) as seen in the rat (13, 33, 34). In addition, MAP was increased significantly by the hyperoxic challenge (21% O2, 95 ± 5, 100% O2, 110 ± 7 mm Hg).

The responses detailed above help substantiate that the laparotomized hamster preparation necessary for monitoring diaphragm PO2m preserves substantial physiological homeostasis as judged by regulation of arterial blood gases, MAP, HR, and hypoxic/hyperoxic responses.

Emphysema, E. The principal differences between C and E hamsters were as follows: (1) Hypoxia reduced HR in E but not C animals. (2) In response to hypoxia, fb did not increase as much in E as in C and consequently, PaCO2 tended to be higher in the hypoxic E hamsters. (3) MAP was not elevated significantly by hyperoxia in E as it was in C hamsters. Taken together, these findings suggest that cardiorespiratory responsiveness was not as great in E as in C hamsters.

Diaphragm PO2m. Under each inspired O2 condition, diaphragm PO2m was lower in E than in C hamsters. This indicates that the Vo2-to-O2 ratio was elevated in E. Radiolabeled microsphere measurements of diaphragm blood flow demonstrate that in the resting animal breathing room air, this variable was not altered significantly in E hamsters (11). Thus, the reduced diaphragm PO2m found herein was due principally to a greater fractional O2 extraction (i.e., increased Vo2-to-O2 ratio) with a modest contribution from the decreased arterial O2 content (Figure 5). Assuming an arterial hemoglobin

Figure 4. Relationship between mean arterial blood pressure and diaphragm microvascular PO2 (PO2m) at 21% inspired O2. Y-intercept was significantly lower for emphysema condition.

Figure 5. Mean arterial and diaphragm microvascular (PO2m) points for O2 and hemoglobin (Hb) saturation in control (C) and emphysematous (E) hamsters. O2 contents estimated from Dill-Gomez relationship (35) are arterial: C, 23.6, E, 18.9; Microvascular O2 content: C, 13.9, E, 7.7 ml/dl.
concentration of 18.3 g/dl (11) and using the Dill–Gomez table (35), arterial O₂ contents of 23.6 and 18.9 ml/dl are calculated for C and E hamsters, respectively. This difference widens substantially for microvascular O₂ content for which the respective values are 13.9 and 7.9 ml/dl. This is consistent with an increased diaphragmatic VO₂ secondary to an elevated work of breathing (lung and airways resistances), possibly increased ventilation, and a mechanically disadvantaged diaphragm in E.

Hypoxia and hyperoxia are expected to affect diaphragm PO₂m via at least two mechanisms: altered diaphragmatic VO₂ consequent to changes in ventilatory muscle work (i.e., increased in hypoxia, decreased in hyperoxia, see Ik in Table 2), and decreased (hypoxia) or increased (hyperoxia) arterial O₂ content. Either of these factors in separate would lower (hypoxia) or raise (hyperoxia) PO₂m and this is precisely what was found with both factors operant (Figure 2).

It must be considered that the diaphragm exhibits considerable structural and functional heterogeneity both between the costal and crural diaphragms and also within the costal diaphragm (36). In the present investigation, as in many others (e.g., 6, 13, 15, 21, 36, 37), we chose to examine the medial costal diaphragm because this region undergoes the greatest absolute shortening and has the largest muscle mass within the costal diaphragm. Consequently, the medial costal diaphragm is likely to support a substantial portion of the inspiratory effort. Whether other diaphragmatic regions demonstrate similar behavior with respect to PO₂m could not be determined from the present investigation.

**MAP and Diaphragm PO₂m**

Diaphragm PO₂m in C and in E hamsters decreased in an approximately linear fashion with reductions in MAP (Figure 4) as demonstrated previously in the rat (13). However, at each MAP, diaphragm PO₂m was significantly lower in E versus C hamsters. Systemic hypotension is a potent ventilatory stimulus (31, 32) and will act to increase breathing and elevate diaphragm VO₂. If diaphragm vascular conductance does not increase commensurate with this increased VO₂, diaphragm PO₂m must fall and this is exactly what was found. At any given MAP, the lower diaphragm PO₂m in E versus C hamsters is again consistent with greater ventilatory muscle demands and elevated VO₂.

**Pattern of Ventilatory Muscle Recruitment in Emphysema and Chronic Obstructive Pulmonary Disease (COPD)**

With progressive hyperinflation, the mechanical efficacy of the diaphragm is impaired which necessitates increased participation of the so-called accessory muscles to sustain the ventilatory effort. Thus, despite elevated neural drive to the diaphragm in patients with COPD (38), inspiratory discharge frequencies also increase for the parasternal intercostals and scalene muscles (39). In support of a greater recruitment and ventilatory participation of accessory muscles in emphysema, an elegant structural and functional analysis of the hamster medial scalene muscle has identified adaptations consistent with elevated recruitment. Specifically, Fournier and Lewis (40) documented elevated inspiratory electromyographic activity of the medial scalene muscle and an altered expression of myosin heavy chains (2A increased, 2X decreased) in concert with reciprocal changes in the proportion of Type IIA (increased) and IIX (decreased) fibers. In addition, oxidative enzyme activity (assessed via succinate dehydrogenase) was elevated 50–63% in all fibers of the medial scalene. From the above, it is apparent that the recruitment of the diaphragm in emphysema is increased, however, in the face of geometric impediment to the generation of useful inspiratory work by the diaphragm, greater recruitment and participation of accessory inspiratory muscles (i.e., parasternal intercostals, scalene) are necessary. The reduced diaphragm PO₂m reported herein is consistent with greater diaphragm recruitment and contractile activity in the absence of commensurately increased O₂ delivery (11).

**Pathophysiological Implications of Lowered Diaphragm PO₂m in Emphysema**

Blood-tissue O₂ transfer within the diaphragm may be described by Fick’s law: \( VO₂ = DO₂m (PcO₂ - PiO₂) \), where DO₂m is the effective diffusing capacity for O₂ and PcO₂ and PiO₂ are mean capillary and intracellular PO₂s, respectively. The present investigation has demonstrated that diaphragm PO₂m, which is our estimate of PcO₂, is ~35% lower in E hamsters compared to C hamsters. Consequently, to achieve a given VO₂ (or more reasonably, an elevated VO₂) in the E condition, either DO₂m must increase or PiO₂ decrease or both. There is morphometric evidence that E stimulates capillary neogenesis (6, 19) thereby elevating capillary length and surface area per fiber volume ~14% (6), which would be expected to elevate DO₂m to the extent that the increased capillary surface area could be recruited for O₂ exchange. Because this increase is only a modest fraction (less than half) of the fall in PO₂m (and by extension PCO₂), a fall in PiO₂ would be expected to occur in order to facilitate the required VO₂. At a given VO₂, a decreased PiO₂ would elevate perturbations of [ADP] and [PCr] (23). This, in turn, will act to accelerate glycolysis and utilization of very limited intramuscular glycogen reserves. We speculate that in E, the reduced diaphragm PO₂m may decrease PiO₂ and exacerbate muscle glycogen depletion thereby contributing to or causing diaphragm fatigue and failure. If this is indeed the case, adaptations of oxidative capacity may prove essential to preserving diaphragm function in the patient with emphysema. Specifically, treatment modalities such as exercise training that elevate skeletal muscle oxidative capacity result in a reduced disturbance of intramyocyte [ADP] and [PCr] for any given VO₂ (41). Consequently, the beneficial effects of exercise or specific respiratory muscle training undertaken by patients with COPD may arise in part from: (1) elevated diaphragm oxidative capacity-associated reductions in [ADP] and [PCr] perturbation and an associated decrease of glycogenolysis, and (2) potential improvement of O₂ delivery via alterations of diaphragm capillarity, which may elevate diaphragm O₂-diffusing capacity (DO₂m) and constrain the reduction of diaphragm PO₂m observed herein.

**Acknowledgment:** The authors are indebted to Professor David F. Wilson and Dr. Sergei Vinogradov for assistance with the phosphorescence quenching technology. In addition, the technical assistance of Ms. Janet A. Bailey, Holly K. Brown, and Crystal M. Geer is gratefully acknowledged.

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