Does an acute COPD crisis modify the cardiorespiratory and ventilatory adjustments to exercise in horses?


The present study was conducted to understand the mechanisms leading to the decrease in exercise capacity observed in horses suffering from chronic obstructive pulmonary disease (COPD). Five COPD horses were submitted to a standardized submaximal treadmill exercise test while they were in clinical remission or in acute crisis. Respiratory airflow, O$_2$ and CO$_2$ fractions in the expired gas, pleural pressure changes and heart rate were recorded, and arterial and mixed venous blood were analyzed for gases tensions, hemoglobin, and plasma lactate concentrations. O$_2$ consumption, CO$_2$ production, expired minute ventilation, tidal volume, alveolar ventilation, cardiac output, total pulmonary resistance, and mechanical work of breathing were calculated. The results showed that, when submaximally exercised, COPD horses in crisis were significantly more hypoxemic and hypercapnic and that their total pulmonary resistance and mechanical work of breathing were significantly higher and their expired minute ventilation significantly lower than when they were in remission. However, their O$_2$ consumption remained unchanged, which was probably due to the occurrence of compensatory mechanisms, i.e., higher heart rate, cardiac output, and hemoglobin concentration. Last, their net anaerobic metabolism seemed to be more important.

CHRONIC OBSTRUCTIVE pulmonary disease (COPD) is a common condition encountered in horses and is generally associated with chronic cough, bronchial hypersecretion, and dyspnea. It is a clinical entity specific to horses, somewhat similar to human asthma because of its allergic etiology but showing clinical similarities to human chronic airflow obstruction.

This respiratory disorder is most frequently observed in mature subjects, which are riding horses mainly used for jumping, endurance, eventing, and dressage, and compared the results with healthy horses. They reported different adjustments according to the breed of the horses, i.e., increase in red blood cell volume in relation to body weight and restricted V$_E$ in standardbreds and excessive HR response in saddlebreds. Unfortunately, they did not measure arterial blood-gas tensions during exercise, and an objective assessment of the pulmonary functional modifications of their COPD horses at rest was not reported. Another study by Kvart et al. (16) reported no significant differences in arterial blood-gas tensions in COPD horses exercising either after being kept on straw bedding and fed hay or after being fed silage and kept in a dust-free environment. In this study as in the previous one, no information about the clinical status of the horses at the time of the tests was available. In humans, a limited exercise capacity is also a major feature of chronic airflow obstruction. Many factors contribute to this limitation: some of them are now understood, and others are still the subject of controversy. It seems that human COPD subjects are limited during exercise by their ventilatory apparatus rather than by their cardiovascular system (25). Most of the work has led to the conclusion that the inadequacy of the ventilatory response of COPD patients (3), the mechanical constraints due to airflow obstruction (13), the excessive cost of breathing, i.e., >40% of the total exercise V$_O_2$ (17), and hence the fatigue of the inspiratory muscles (11), are probably the main determinants of reduction in their exercise tolerance. Moreover, in severely hypoxic patients, O$_2$ availability apparently limits intramuscular oxidative metabolism because hypoxemia increases the net anaerobic metabolism for ATP production (19).

It is well known, however, that the respiratory adjustments to exercise of healthy humans and healthy horses are quite different. The same discrepancies may consequently be expected as regards the exercise-induced adaptations in subjects suffering from chronic airflow obstruction, and, therefore, it would be hazardous to extrapolate the observations made in humans to the horse.

The present study was conducted to understand better the mechanisms leading to the decrease in exercise capacity observed in COPD horses. A direct measurement of the gas exchange and the horse's V$_O_2$ and V$_E$ during a submaximal exercise. Therefore, ventilatory
and cardiorespiratory measurements as well as arterial and mixed venous blood-gas tensions were measured during a standardized treadmill exercise test in COPD horses while they were either in clinical remission (R) or in acute crisis (C).

**MATERIALS AND METHODS**

**Horses**

Five saddlebred horses [weight 552.4 ± 13.1 (SE) kg; age 10.6 ± 1.4 yr] with a history and clinical signs of COPD were used. One month before the experiment, they underwent a thorough clinical examination, including electrocardiogram, arterial blood-gas analysis, hematology, endoscopy of the airway, tracheobronchial lavage, and pulmonary scintigraphy. This allowed the diagnosis to be made that they suffered from COPD and were free of any other health problems.

For 1 mo, they were housed in well-ventilated stables on wood shavings and received good-quality oats as concentrates and grasslage as forage. They did not receive any treatment during the 15 days preceding the experiments. During this period, they were trained daily on the treadmill and regularly accustomed to the laboratory procedures.

The training aimed mainly at having the horses calm and in confidence on the treadmill rather than to improve their fitness. Therefore, it consisted in 20 min of work per day, with 5 min of walking, 10 min of trotting with an increasing slope from 0 to 10%, 2 min of galloping (8 m/s at 0% slope), and 3 min of walking again on a flat treadmill.

**Measurements**

Mechanics of breathing. Before the tests, and to control whether they were in the appropriate clinical state, the horses underwent an evaluation of their mechanics of breathing. Esophageal pressure was measured by means of an esophageal balloon catheter made from a condom sealed over the end of a polyethylene catheter (4 mm ID, 6 mm OD, 220 cm long) positioned with its tip in the middle thoracic esophagus and connected to a pressure transducer (Bentley, Trantec M800, Medical Electronic Construction, Charleroi, Belgium). Respiratory airflow was simultaneously measured with a Fleish pneumotachograph no. 4 mounted on a face mask and coupled to a differential pressure transducer (Valydine M145, Validyne Engineering, Northridge, CA) with two identical catheters (4 mm ID, 6 mm OD, 220 cm long). The parameters of mechanics of breathing were immediately calculated by a computerized system (Hemodynamic Respiratory System, Medical Electronic Construction). Calibration of volume was performed with a 2-liter pump, of airflow with a rotameter, and of pressure with a water manometer. Technical details are reported elsewhere (2).

During exercise, esophageal pressure was measured by the same method as described above; the catheter was connected to a pressure transducer (Statham-PD 23, Siemens, Solna, Sweden) and an amplifier (Sirecust 323, Siemens, München, Germany). The signals were simultaneously recorded on paper (Gould ES 1000, Waithier-Braine, Belgium) and on magnetic tape (MTR 3968A, Hewlett-Packard, Brussels, Belgium). Respiratory airflow from each nostril was simultaneously and continuously measured by using two ultrasonic pneumotachographs (Birmingham Research and Development Ltd Flowmetrics, Birmingham, UK). Calibrations were performed by using a water manometer for pressure and a high-flow source and a flow velocity transducer (AVT model 8450/60/70, Bureau Technique Wintgens, Eupen, Belgium) for airflow. The delay between the pressure and airflow signals was determined before each test (1).

Blood measurements. The transverse facial artery was catheterized with a 20-gauge catheter (Baxter, Brussels, Belgium) secured to the skin with glue. A 110-cm plastic extension line was attached to the catheter to allow blood to be drawn at a distance from the horse. The catheter and the extension were flushed with heparinized saline between sampling to maintain patency. I immediately before the collection of each sample, 10 ml of blood and saline were drawn and discarded. Arterial blood samples were withdrawn during the last 5 s of each step of the test into 2-ml syringes, the dead space of which was filled with sodium heparin (10,000 IU/ml). The syringes were capped and stored in crushed ice until analysis, which was performed within a maximum of 15 min after collection.

Blood temperature was measured in the pulmonary artery by using the thermistor of a Swan-Ganz catheter (Electech 73-4067 TF, Columbus Instruments, Columbus, OH) inserted in the left jugular vein through an 8.5-F introducer (no. SI-09875-E, Arrow, Redding, PA) placed in the correct position under pressure control and connected to a cardiac output (Q) computer (CardiowaxI, Columbus Instruments). Mixed venous blood was sampled, via the Swan-Ganz catheter, by using the same procedure and at the same height as arterial blood sampling, into heparinized syringes, as well as into heparin sodium and moniodoacetate tubes for lactate determination (colorimetric method, Boehringer, Ingelheim, Germany).

Arterial and mixed venous PO2 (Pao2 and PvO2, respectively) and PCO2 (PaCO2 and PcCO2, respectively), arterial hemoglobin (Hb), arterial O2 saturation (SaO2), arterial O2 content (CaO2), venous O2 content, as well as arterial and mixed venous pH were measured by using an autocalibrated blood-gas analyzer (AVL 995, VEL, Louvain, Belgium). The blood-gas analyzer was calibrated with standard gases and buffers. Calibrations were automatically performed every 2 h. Adequacy of the calibration was controlled before and after each set of measurement, i.e., a complete experiment of one horse, by using three different tonometered solutions (Confitest III blood-gas control, AVL). Quality control test with equine blood tonometered with gas of known compositions (PO2 and PCO2 of 40 and 100 Torr, respectively) were performed before and after a complete set of experiments, i.e., experiments on five horses. Last, the very first, the middle, and the last arterial and mixed venous blood samples of each test, i.e., a complete experiment of one horse, were analyzed in duplicate, to control the repeatability of the results (i.e., <1- and 0.5-Torr difference between 2 analyses for PO2 and PCO2, respectively). No abnormalities were detected by one of these controls. The data were temperature corrected with the pulmonary arterial blood temperature recorded at the time of the blood sampling.

V02 and carbon dioxide output (VCO2). A mass spectrometer (MGA 2000, Case, Biggin Hill, Kent, UK) was used to sample air in one flow tube. The sampling capillary was positioned 2 cm from the open end of the tube and continually measured O2 and CO2 concentrations in the inspired and expired respiratory gases on a breath-by-breath basis. Airflow signals from each nostril and respiratory O2 and CO2 concentration signals underwent analog-to-digital conversion and were recorded by using a data-acquisition system. Tidal volume (VT), respiratory frequency (f), VE ([BTPS]), VO2 ([STPD]) and VCO2 ([STPD]) were instantaneously calculated by online and breath-by-breath computer analysis (Case, Biggin Hill, Kent, UK). The concept of this method of determination of VO2 was described for the very first time by Beaver et al. (5).
The accuracy of the method of flow measurements by ultrasonic pneumotachographs (7) as well as calculation of VO₂ has been previously assessed (8).

The gas concentration input signals recorded from the mass spectrometer were delayed in time compared with the flow signals because of the transit time of the sample along the sampling cannula of the mass spectrometer. The delay was systematically determined and introduced into the program and was used to synchronize the gas concentration with the flow signal (1). Before and after each test, calibration of the mass spectrometer was performed and controlled by using gas mixtures of known composition.

Measurement of HR. HR values were recorded using a horse tester (Apparatus for Medical Guidance, Dinant, Belgium) throughout each investigation and recovery period: HR was calculated and recorded during consecutive periods of 5 s. After each experiment, the stored data were displayed on a microcomputer.

Experimental Protocol

Horses were tested while in either R or C. The following limits were arbitrarily chosen to classify the horses. For the R group the values were PaO₂ ≥ 85 Torr, maximal pleural pressure changes (ΔPpl_max) ≤ 1.25 kPa, total pulmonary resistance (RL) ≤ 0.080 kPa·l⁻¹·s, and dynamic lung compliance (CL) ≥ 10 l/kPa; and for the C group the values were PaO₂ ≤ 82 Torr, ΔPpl_max ≥ 1.75 kPa, RL ≥ 0.100 kPa·l⁻¹·s, and CL ≤ 8 l/kPa. The tests in remission were performed first. The test in C took place 1 wk later after the horses were placed on straw and mouldy hay to induce bronchoconstriction by natural challenge. The period of exposure was adapted to the individual response. It took from 4 to 24 h to obtain a C sufficient to lead the horses outside the norm of ranges of pulmonary function previously mentioned.

Run up to fatigue. Before the first test and after the second one, a rapid incremental test was performed on the treadmill with a slope at 0% to determine maximal VO₂ (VO₂max) in R and in C. A 5-min warm-up period at 3.0 m/s was followed by 1-min stages at 4, 8, 9, 10, and 11 m/s. The VO₂ reached when the horses stopped running despite encouragement was considered as peak VO₂ (VO₂peak) rather than as VO₂max, because no plateau was observed and HR was most probably not maximal. The numbers of steps completed during this test was expressed as the number of the complete steps plus a decimal equivalent on the basis of the number of seconds before completion of a full step.

Standardized submaximal test (SST). The horses were catheterized and instrumented out of the laboratory. The tests were performed on a treadmill (Equispeed, Versailles, MI) located in a laboratory where the temperature and the relative humidity were kept constant (15°C and 55–60%, respectively). After an 8-min warm-up (5-min walk and 3-min trot on the level), the SST consisted of 7-min exercise of increasing intensity at 4.2 m/s, with a slope of 2, 4, 6, 8 (1 min each for each step), and 10% (3 min). The treadmill was then lowered to 0%, and the horses trotted for 2 min more before being stopped.

Arterial and venous blood were sampled during the last 5 s of each minute of the SST. Ventilatory and cardiorespiratory measurements were continuously measured during the SST and were simultaneously recorded by the computer, on a 12-channel rapid writing polygraph (Gould ES 1000) at a paper speed of 10 mm/s during the whole test and at 50 mm/s during the last 15 s of each step, and on a magnetic tape recorder (Hewlett Packard).

Calculations and Statistical Analysis

Data are reported as means ± SE. Most of the results were collected during the last 15 s of the last step of the incremental SST (3rd min at 4.2 m/s with 10% slope).

On the paper recording at 50 mm/s, ΔPpl_max i.e., pleural pressure (Ppl); maximal airflow (V) changes, i.e., the flow changes between peak inspiratory and expiratory flows; the mechanical work of breathing (Wrm), i.e., the area enclosed in the Ppl-Vt loop; and RL, i.e., the ratio of the V changes to the Ppl changes at isovolume 50%, were calculated (1). The accuracy of the method of flow measurements by ultrasonic pneumotachographs (7) as well as calculation of V̇O₂ has been previously assessed (8).

RESULTS

Pulmonary Function Tests at Rest

The results of the pulmonary function tests obtained at rest before the tests in R and C were started are given in Table 1.

Run Up to Fatigue

When performing the run up to fatigue, the horses in R reached a mean VO₂peak and peak HR of 92.8 ± 5.5 ml·kg⁻¹·min⁻¹ and 197.7 ± 5.7 beats/min, respectively. In horses in C, these values were 93.7 ± 4.5 ml·kg⁻¹·min⁻¹ (not significantly different from R) and 206.5 ± 7.6 beats/min, respectively (significantly different from R). The maximal number of steps was 4.95 ± 0.6* in R and 206.5 ± 0.20 in C, which means that the horses reached VO₂peak 30 s earlier when they were in C and were unable to keep the speed, once this peak was reached.

Table 1. Pulmonary function tests performed at rest before treadmill exercise test, to assess that the horses were in the appropriate clinical state, i.e., remission or crisis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Remission</th>
<th>Crisis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔPpl_max, kPa</td>
<td>0.93 ± 0.1</td>
<td>3.0 ± 0.7*</td>
</tr>
<tr>
<td>CL, l/kPa</td>
<td>10.6 ± 2.1</td>
<td>3.1 ± 0.6*</td>
</tr>
<tr>
<td>RL, kPa·l⁻¹·s</td>
<td>0.065 ± 0.010</td>
<td>0.208 ± 0.035*</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>17.1 ± 2.8</td>
<td>17.5 ± 3.1</td>
</tr>
<tr>
<td>Vt, liters</td>
<td>5.6 ± 0.8</td>
<td>5.9 ± 1.0</td>
</tr>
<tr>
<td>Ve, l/min</td>
<td>91.1 ± 14.5</td>
<td>97.0 ± 17.7</td>
</tr>
<tr>
<td>PaO₂, Torr</td>
<td>92.2 ± 4.5</td>
<td>77.5 ± 2.8*</td>
</tr>
<tr>
<td>PaCO₂, Torr</td>
<td>42.3 ± 2.0</td>
<td>46.0 ± 1.7</td>
</tr>
</tbody>
</table>

Values are means ± SE for 5 horses. ΔPpl_max, maximal pleural pressure change; CL, dynamic lung compliance; RL, total pulmonary resistance; f, respiratory frequency; Vt, tidal volume; Ve, expired minute ventilation; PaO₂, arterial PO₂; PaCO₂, arterial PCO₂. *Significantly different from remission, P < 0.05.
Table 2. Cardiorespiratory parameters collected from COPD horses in remission or in crisis during the highest intensity of a standardized treadmill test

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Remission</th>
<th>Crisis</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂, ml·kg⁻¹·min⁻¹</td>
<td>77.6 ± 3.9</td>
<td>83.2 ± 3.1</td>
</tr>
<tr>
<td>VCO₂, ml·kg⁻¹·min⁻¹</td>
<td>81.2 ± 3.8</td>
<td>101.9 ± 4.3*</td>
</tr>
<tr>
<td>RQ, I/l</td>
<td>1.04 ± 0.01</td>
<td>1.23 ± 0.06*</td>
</tr>
<tr>
<td>Ve, l/min</td>
<td>1.278 ± 97</td>
<td>1.101 ± 33*</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>75.2 ± 5.2</td>
<td>62.3 ± 3.4*</td>
</tr>
<tr>
<td>VT, liters</td>
<td>17.7 ± 1.9</td>
<td>18.7 ± 1.4</td>
</tr>
<tr>
<td>V̇a, l/min</td>
<td>745.5 ± 60.3</td>
<td>699.2 ± 30.5</td>
</tr>
<tr>
<td>Vo, l/min</td>
<td>532.5 ± 410</td>
<td>401.6 ± 26.1*</td>
</tr>
<tr>
<td>Vo/VT, %</td>
<td>41.7 ± 12</td>
<td>36.5 ± 2.0*</td>
</tr>
<tr>
<td>Ve/V̇O₂, l/l</td>
<td>30.0 ± 1.7</td>
<td>24.0 ± 1.0*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>193 ± 3</td>
<td>204 ± 3*</td>
</tr>
<tr>
<td>Q, l/min</td>
<td>235.9 ± 15.6</td>
<td>264.3 ± 17.8*</td>
</tr>
<tr>
<td>V̇a, l/min</td>
<td>1.221 ± 0.081</td>
<td>1.294 ± 0.072</td>
</tr>
<tr>
<td>ΔPplmax, kPa</td>
<td>6.83 ± 0.42</td>
<td>8.32 ± 0.54*</td>
</tr>
<tr>
<td>ΔVmax, l/l</td>
<td>114.7 ± 6.9</td>
<td>104.0 ± 4.7*</td>
</tr>
<tr>
<td>Rl, kPa·l⁻¹·s</td>
<td>0.054 ± 0.006</td>
<td>0.085 ± 0.005*</td>
</tr>
<tr>
<td>Wrm, J</td>
<td>81.5 ± 12.3</td>
<td>119.5 ± 17.8*</td>
</tr>
<tr>
<td>WrmV̇E, l/l</td>
<td>4.65 ± 0.42</td>
<td>6.65 ± 0.65*</td>
</tr>
<tr>
<td>WrmV̇E, l/min</td>
<td>6.167 ± 620</td>
<td>8.186 ± 800*</td>
</tr>
<tr>
<td>WrmV̇O₂,l/O₂</td>
<td>130 ± 11</td>
<td>174 ± 16*</td>
</tr>
</tbody>
</table>

Values are means ± SE for 5 horses. COPD, chronic obstructive pulmonary disease; VO₂, oxygen consumption; VCO₂, carbon dioxide output; RQ, respiratory quotient; f, respiratory frequency; V̇a, alveolar ventilation; V̇d, dead space ventilation; V̇o, dead space volume; HR, heart rate; Q, cardiac output; V̇s, stroke volume; ΔV̇max, maximal peak airflow change during 1 breathing cycle; Wrm, mechanical work per breath; WrmV̇E, mechanical work per liter; WrmV̇O₂, mechanical work per liter of O₂ consumed.

*Significantly different, P < 0.05.

Standardized Submaximal Test

The cardiorespiratory and ventilatory measurements collected during the last step of the standardized submaximal test (trot at 4.2 m/s and 10% slope) in R and C are reported in Table 2. Ve of the horses in C condition was significantly lower than in R condition. This was due to a significantly lower f, which was not counterbalanced by the small and insignificant increase in VT. Although the ventilation was reduced, the VO₂ was not significantly different from one condition to the other. By contrast, the VCO₂ and hence the respiratory quotient were higher in C conditions. The ventilatory equivalent for O₂ was lower in C than in R. HR and Q at the highest intensity and plasma lactate concentration at the end of the test were higher in C conditions than in R conditions.

The V̇a in C was maintained at a level almost similar to the level observed in R, whereas the V̇o/VT ratio and dead space ventilation (V̇d) were significantly lower in C. Last, Rl, ΔPplmax, and Wrm per cycle, per liter, per minute, and per liter of O₂ consumed were significantly higher in C condition. When the horses were in C, Rl decreased significantly from rest to exercise.

Table 3 gives the results of the blood analyses and particularly the PO₂ and PCO₂. The horses were significantly more hypoxemic and hypercapnic when exercised in C. Additionally, PV̇O₂ was lower and PV̇CO₂ higher in C condition. The arterial-mixed venous differences in PCO₂ and the alveolar-arterial difference in PO₂ were the same in both conditions, while the arterial-mixed venous difference in PO₂ was lower in crisis (Fig. 1). Hb saturation was lower in C, but, because of a higher arterial concentration in Hb, the CaO₂ was not significantly different.

DISCUSSION

As suspected, most of the exercise-induced adjustments observed in COPD horses were totally different from those previously reported in humans. In exercising COPD men, two clinical syndromes have been determined according to whether pulmonary emphysema or chronic bronchiolitis is the predominant factor, i.e., subjects are either hyperoxic or "pink and puffing," or hypoxic or "blue and bloated," respectively (13). In horses, diffuse pulmonary emphysema (which induces hyperoxia during exercise) is rarely observed: our horses were all hypoxic. In COPD men, Ve at a given VO₂ was increased (3). This increase in Ve is achieved by an increase in flow and f while V̇t is maintained constant (11). Conversely, in the present study, the COPD horses in C had a lower Ve, mainly because they had a lower f. In humans, ventilatory equivalents for O₂ and CO₂ as well as VO₂/VT are reported to increase (14), whereas the opposite was observed in our horses.

The plasma lactate concentration was slightly but significantly higher in the COPD horses in C than in R. Because lactic acid ultimately results in VCO₂, this could partly explain why VCO₂ was significantly higher during C. However, this difference in lactate is too low to be responsible for the entire increase in VCO₂ in C. An increase in lactate has also been observed in exercising humans with COPD (18). In humans, an impairment of oxidative phosphorylation, an early activation of anaerobic glycolysis, and a decrease in activities of mitochondrial...
drial enzymes have been put forward to explain this observation (18), although a number of other factors, such as inappropriate O2 delivery to the working muscles or reduction in lactate clearance, may also be involved in this increase in lactate production. Other authors have also suggested that this phenomenon could be the reflection of a general state of unfitness (20). This hypothesis can, however, be ruled out in the present work. With the same horses being compared at a 1-wk interval, their fitness should be unchanged from one test to the other.

Exercise-Induced Hypercapnia and Hypoxemia in COPD Horses in C

Exercise-induced hypoxemia is a well-known phenomenon occurring, even in healthy horses, once the intensity of exercise exceeds 60% of VO2max (4). Several explanations have been advanced for the occurrence of this phenomenon, including a mismatch of the ventilation-perfusion ratio (V/Q), diffusion limitation, right-to-left shunts, and a relative alveolar hypoventilation or, rather, a lack of compensatory hyperventilation (4). In the present study, the horses were hypoxemic and hypercapnic in both conditions but this trend was significantly more severe in C than in R. The same factors as those cited above in this paper were probably responsible for the gas-exchange impairment in COPD horses in C, but their relative contribution to hypoxemia and hypercapnia could have been different than in healthy subjects.

Diffusion limitation is one of the main reasons for hypoxemia during heavy exercise in healthy horses, being responsible for a large proportion, i.e., from 55% (22) to 70% (30), of the widening in PAO2-PaO2 difference. Consequently, this factor could have been responsible for the more severe hypoxemia occurring in COPD horses in C. However, although the absolute values of PAO2 and PaO2 were lower in C, the PAO2-PaO2 difference was not different in C compared with R (Fig. 1). This suggests that diffusion limitation was not more severe in C than in R.

The lack of compensatory hyperventilation has been demonstrated to be an important factor contributing to the exercise-induced hypoxemia of healthy horses (4). In the present study, the V̇E of the horses in C was significantly lower than that in R. Because in the same time, V̇D and VD/VT were lower, V̇A was not significantly decreased by C. However, although maintained at the same level in C as in R, V̇A was obviously too low to ensure an appropriate CO2 removal when the horses were in C. The question of the origin of the source of this greater V̇CO2 while V̇O2 is the same in both conditions now requires addressing.

Last, hypoxemia may be related to V/Q inadequacy. Actually, information about exercise-induced modifications of V/Q ratio in horses has been rather conflicting. On the basis of the multiple inert-gas elimination technique, this ratio has been demonstrated to remain quite adequate during maximal exercise in healthy horses (31) or to be slightly impaired (27) and, last, to be significantly worsened, accounting for 41% of the exercise-induced hypoxemia (22). COPD horses in C at rest suffer from V/Q inadequacy (29). Further studies are now necessary to assess whether this inadequacy is further exacerbated with exercise or whether the exercise-induced adjustments ultimately recruits unperfused capillaries and consequently decreases V̇O2.

Compensatory Mechanisms in Submaximally Exercised COPD Horses

Despite the lower ventilation and the more severe hypoxemia, V̇O2 was the same in C and in R. A lack of
relationship between the severity of hypoxemia and reduction in power output has also been observed in humans suffering from chronic airflow obstruction (13) and in horses suffering from idiopathic laryngeal hemiplegia (9).

The fact that \( V_{\text{O}_2} \) was the same in both C and R suggests that, in COPD horses in C, there were compensatory mechanisms that allowed these horses to maintain an adequate \( V_{\text{O}_2} \) during submaximal exercise.

From a ventilatory point of view, although \( V_{\text{E}} \) was lower, ventilation was optimized by the lowering of \( V_{\text{O}} \) and \( V_{\text{O}/V_{\text{T}}} \). The lowering of \( f \), increasing the time period between two breaths, probably improved \( O_2 \) extraction from the inspired air as assessed by the lower \( V_{\text{E}}/V_{\text{O}_2} \).

At the level of blood-gas transport, at least two mechanisms occurred in C to balance the impairment of gas exchange. The first was the significant increase in Hb concentration, which allowed the \( Cao_2 \) to remain the same as in R despite the lower \( SaO_2 \) and \( PaO_2 \). The second was the increase in HR leading to a higher \( Q \), which in turn counterbalanced the lower arterial-mixed venous \( O_2 \) content difference resulting in the same \( V_{\text{O}_2} \).

Despite the fact that these compensatory mechanisms should reach a limit when the horse approaches its maximal exercise capacity, our horses’ \( V_{\text{O}_2}\text{peak} \) values seemed to be unaffected by the C. However, the \( V_{\text{O}_2}\text{peak} \) in C was reached at a lower workload than in R. Further studies are necessary to understand why \( V_{\text{O}_2}\text{peak} \) was independent of the respiratory status of the horses.

Mechanical Cost of Breathing

\( R_L \) was significantly higher in C. Moreover, mechanical work per minute \( V_{\text{E}} \) and \( \Delta P_{\text{pl max}} \) recorded during the last step of the tests in C (6.65 ± 0.65 kPa/l and 8.32 ± 0.53 kPa, respectively) reached and even exceeded the values previously recorded in thoroughbred horses galloping at \( V_{\text{O}_2}\text{max} \) (6.22 ± 0.43 kPa/l and 8.23 ± 0.58 kPa, respectively) (1). However, the COPD horses had a smaller \( V_{\text{E}} \) (1,585 ± 45 l/min in the thoroughbred vs. 1,101 ± 33 l/min in the COPD horses), suggesting an excessive and less efficient recruitment of the respiratory muscles when COPD horses worked, even submaximally. In humans suffering from severe chronic airflow obstruction, it has been reported that the cost of breathing may easily reach 40% of the total exercise \( V_{\text{O}_2} \) (17). To estimate the energetic cost for the consumption of 1 liter \( O_2 \) in our horses, the \( W_{\text{r m}} \) per minute was related to \( V_{\text{O}_2} \). The energetic cost per liter \( O_2 \) was equal to 130 ± 11 and 174 ± 16 J/l \( O_2 \) in R and C respectively, this ratio being consequently 33% higher when the horses were in C, an expected result, taking into account the increase in the resistive work and the fact that these horses could also suffer from true changes in the elastic properties of their lungs (28). Nevertheless, if the caloric equivalent for \( O_2 \) is considered as being equal to 5.04 kcal/l \( O_2 \) (or 21,118 J/l), one may extrapolate that the energetic cost of ventilation represented 6 and 8% of the total \( V_{\text{O}_2} \) in R and C, respectively, which may be considered as negligible. However, it is well known that the estimation of \( W_{\text{r m}} \) by the measurement of the area enclosed by the pressure-volume loop considerably underestimates the total work of breathing because it does not take into account the work done in compressing and decompressing gas in the lungs, the flow-resistive and elastic work done against the thorax, or the work due to chest wall distortion (26). Moreover, estimates of the mechanical efficiency of the respiratory muscles in humans, i.e., the effective mechanical work per minute to \( V_{\text{O}_2} \) of the respiratory muscles (\( V_{\text{O}_2}\text{resp} \)), were only 3–10% (23). If these efficiency percents are the same in the horse, the estimation of the relative cost of breathing should approach 6% (to 18% if efficiency is only 3%) in R and 8% (up to 25% if efficiency is only 3%) in C. Therefore, one may expect that the actual energetic needs for breathing may reach a nonnegligible percentage of the total energetic expenditure during high-intensity exercise in COPD horses in C. Consequently 1) respiratory muscle fatigue would occur earlier in this condition and 2) the \( V_{\text{O}_2}\text{resp} \) would be higher in C at the expense of the \( V_{\text{O}_2} \) of the locomotor muscles. The latter will consequently require more important net anaerobic metabolism to meet their energy needs, which could partly explain the slightly higher lactate concentration.

It has already been suggested that, in healthy horses during strenuous exercise, the \( V_{\text{O}_2}\text{resp} \) reaches a substantial percentage of \( V_{\text{O}_2} \) and that, in this species as in humans, there is a “critical level of ventilation” above which any further increase of \( V_{\text{O}_2} \) would be entirely consumed by the respiratory muscles (1). Because the \( V_{\text{O}_2}\text{resp} \) is higher during a COPD crisis, the critical level is in turn probably lowered in these conditions and consequently reached at a lower exercise intensity than in normal conditions. This could explain the fact that despite 1) its more severe hypoxemia and hypercapnia, 2) its relative hypoventilation in regard to its \( V_{\text{C}_O_2} \), and 3) its potential ability to ventilate more, as assessed by the data obtained in R, the horse in C sets its ventilation at a lower level, mainly by decreasing its \( f \). Dempsey (10) postulated that this special exercise adjustment could occur when the respiratory motor output or drive is not sufficiently augmented because of a strong feedback inhibition signal coming from the over stressed chest wall to the brain stem. Why this special adjustment occurs through a reduction of \( f \) rather than \( V_{\text{T}} \) may be explained by the constraint of minimum average force of the respiratory muscles, which is an important determinant in the control of \( f \) (21). At a given \( V_{\text{E}} \) and with given characteristics of the respiratory system (\( R_L \) and \( C_L \)), a particular \( f \) would be least costly in terms of work of breathing. In the present work, \( R_L \) was higher in C; therefore, \( f \) was lower, probably to reduce the flow-resistive work of breathing. The fact that there was no compensating increase in \( V_{\text{T}} \) could be explained by the modification of the elastic properties of the lungs, as assessed by the reduction of \( C_L \) measured before the test. In this condition an increase of \( V_{\text{T}} \) would have increased disproportionately the elastic work of breathing.
When the horses were in C, their Rl decreased significantly once they started to work (from 0.20 ± 0.05 kPa·l⁻¹·s⁻¹ at rest to 0.085 ± 0.005 kPa·l⁻¹·s⁻¹ during the last step). This observation has already been reported in asthmatic humans, in whom in the few first minutes of work there is bronchodilation manifested by a decrease in airflow resistance (20). This phase is thought to be due to catecholamine release in response to the stress of physical exercise. This physiological adjustment does not occur in healthy horses as reported in a previous study (1) or in the COPD horses when they were in remission. This is explained by the fact that in these animals there is no bronchomotor tone as assessed by previous studies that showed that bronchodilators have no influence on the mechanics of breathing in healthy horses and in COPD horses in R (6).

Exercise Intolerance in COPD

Two types of tests were performed in this study, i.e., a run up to fatigue and a standardized submaximal test. The first test has been performed to try to determine VO₂max, to express the intensity of exercise of the second test in terms of relative workload. Unfortunately, for unknown reasons, the COPD horses were obviously unable to run fast enough to reach their maximal oxidative capacity. In both conditions, i.e., C and R, they stopped to run while reaching the same level of VO₂, which has been termed VO₂peak in the present work. Nevertheless, VO₂peak was reached earlier when they were in C, suggesting a decrease in resistance to exercise. The same observations have been made in humans suffering from chronic airflow obstruction who stopped to work at submaximal HR and submaximal ventilation, making it difficult to isolate the real limiting factor. Killian et al. (15) suggested that exercise tolerance in this case was more related to individual behavior and motivation than to true physiological modifications.

On the other hand, all the horses were able to complete the submaximal tests, even when in C. However, the tests in C were obviously more difficult to perform and necessitated encouragement of the horses, especially at the end of the test. It was surprising that their VO₂ was not different especially at the end of the test. It was surprising that performance and necessitated encouragement of the horses, ever, the tests in C were obviously more difficult to complete the submaximal tests, even when in C. How- nevertheless, the present work led to the suggestions that exercise intolerance in heavily exercising COPD horses could occur because 1) the compensatory mechanisms are probably overwhelmed during high-intensity exercise, VO₂max is probably reduced and reached earlier, and time to fatigue shortened, leading to an earlier occurrence of exhaustion; 2) the mechanical work of breathing is higher during C and may induce respiratory muscle fatigue, then respiratory discomfort, and finally exercise intolerance; and 3) the higher level of blood lactate during exercise in C probably leads to an earlier occurrence of metabolic acidosis when the effort is further prolonged or intensified.

In conclusion, this work has shown that, when COPD horses in C perform a submaximal exercise, they are more hypoxemic and hypercapnic and they have a lower ventilatory level than when they are in R. Their net anaerobic metabolism is slightly higher. Their VO₂ remains unchanged, which is probably due to the occurrence of compensatory mechanisms, such as a better ventilatory equivalent for O₂, a higher HR and Q, and a higher Hb concentration.

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