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Evaluating the pulmonary function test and concentration of acute phase proteins in foals with respiratory distress syndrome (RDS)

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ABSTRACT

The present study aims to evaluate pulmonary function tests and acute phase proteins in foals with respiratory distress syndrome (RDS) compared to apparently healthy foals. A total of 26 foals of both sexes collected from different farms at Sharqia Governorate, Egypt, were used in the present study. Seven foals were clinically healthy defined as a control group; showed no current or previous respiratory illness, and had normal blood hematology and biochemistry parameters. Nineteen foals presented with signs of respiratory distress syndrome, including increased body temperature, pulse, and respiratory rate, cough either on stimulation (37%) or spontaneous (63%), on auscultation of the lung there was exaggerated vesicular sound (32%), wheezing (37%), pleuritic frictional sound (26%) and absence of lung sound (26%). Hemoglobin, total protein, and albumin were decreased significantly in RDS foals compared to healthy foals. While, a significant increase in packed cell volume, erythrocytes, leucocytes, platelets, and neutrophils percent in RDS foals compared to healthy foals was observed. The RDS foals showed a significant reduction in blood pH and partial pressure of oxygen, base excess, and a significant increase in partial pressure of carbon dioxide and bicarbonate compared to healthy foals. Acute phase proteins showed a significant increase of SAA, haptoglobin, fibrinogen, and procalcitonin in RDS foals compared to healthy control foals. It is concluded that assessing pulmonary function tests and APPs concentration may serve as effective and early diagnostic tools for identifying foals affected by RDS.

1. INTRODUCTION

Respiratory disease is one of the main causes of morbidity and mortality in neonatal horses, which frequently affects newborn foals and weanlings (Reuss and Cohen, 2015). Neonatal foals frequently develop neonatal pneumonia, a serious condition that can arise at the time of delivery and is frequently linked to septicemia (McKenzie, 2018; Reuss and Cohen, 2015). It is mostly caused by the invasion of foreign microbes that enter the body through the umbilicus, digestive tract, or respiratory system (Lavoie et al., 1994). A systemic inflammatory response syndrome may be brought on by this invasion, and it may be manifested as generalized or specific symptoms like lung injury or respiratory distress (Reuss and Cohen, 2015). Respiratory distress syndrome is characterized by the presence of tachycardia and tachypnoea in all foals, with fever (Dunkel et al., 2005). Any respiratory dysfunction can lead to a decrease in ventilation and gas exchange. Therefore, respiratory illnesses frequently contribute to exercise intolerance and poor performance. This is one of the problems that equine internists encounter most frequently (Kozłowska et al., 2022).

The early detection and monitoring of lung inflammation in veterinary medicine is a significant challenge. Sepsis is one of the main causes of neonatal foal death in horses. As a result, there is a greater need to examine inflammation biomarkers, such as acute phase proteins, to determine their value as a precursor to sepsis and to manage the efficacy of treatment in foals with bacterial pneumonia (Pusterla et al., 2006). Procalcitonin has a pathophysiologic role as an inflammatory mediator increased in inflammatory processes in the lung (Barton et al., 2016).

Serum amyloid A (SAA) measurement is considered an indicator of acute inflammation and a useful monitoring tool for clinically ill horses, with diagnostic accuracy superior to white blood cell count and fibrinogen (Johns and Heller 2020). Other clinical parameters, such as blood gas analysis, are also thought to be crucial diagnostic indicators for pneumonia, assisting with early treatment choices.

We hypothesized that measuring the acute phase proteins and pulmonary function test would provide a good prognostic outcome of the disease in foals compared to other clinical variables. This study aimed to evaluate the pulmonary function test and acute phase protein as diagnostic tools for RDS in foals.

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2. MATERIAL AND METHODS

2.1. Animals and ethical statement

A total of 26 foals of both sexes aged from 7 – 12 months, collected from different farms at Sharqia Governorate, Egypt, were used in the present study. Seven foals were clinically healthy and were used as a control group; they had a history of absence of respiratory signs. Nineteen foals were presented with signs of respiratory distress syndrome. The current investigation received approval from the Institutional Animal Care and Use Committee at the Faculty

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of Veterinary Medicine, Zagazig University, Egypt (ZU-IACUC/2/F/138/2023).
Samples were collected from foals (n = 19) showing symptoms like fever, cough, nasal discharge, congested visible mucous membranes, and abnormal auscultation of the thorax. Diseased foals were diagnosed based on the laboratory, clinical, and postmortem findings. In addition, samples were obtained from healthy foals (n = 7) that presented with no history of previous illness and/or vaccination. After collection, blood samples were packed in an ice tank and transported immediately to the laboratory for analysis.

2. 2. Clinical examination

A comprehensive physical examination was conducted on all foals in this study. Vital signs such as body temperature, respiration, and heart rate were recorded. Tactile stimulation of the larynx and trachea causes cough reflex in foals. Additionally, lung auscultation was performed on each foal according to Constable et al. (2017).

2.3. *Sample collection*

Two venous blood samples were obtained from the jugular vein before the initiation of therapy for the assessment of hematological and biochemical parameters. The first blood sample was collected in tubes containing ethylene-diamine-tetra-acetic acid (EDTA) anticoagulant to measure complete blood count parameters, including hematocrit (%), hemoglobin (g/dl), erythrocyte count ($\times10^6$/µl), and total leukocyte count ($\times10^3$/µl), using an automated cell counter (HA-Vet Hematology Analyzer®, Clindiag Systems B.V.B.A, Belgium).
The second sample was placed in a plain tube without anticoagulant to collect serum. Afterward, the samples underwent centrifugation at 3000 rpm for 10 minutes. The resulting serum was then collected and stored frozen at -20°C until further analysis. Serum used for biochemical analysis including the assessment of total protein and albumin levels. This analysis was conducted using the Beckman AU5800 analyzer (Beckman Coulter, California, USA).

2.4. Blood gas analysis

An arterial blood sample was obtained from the right common carotid artery puncture hand fest above the shoulder joint in the distal third of the neck between the trachea and the jugular vein, using heparinized syringes. A strong pressure with closed fist should be kept on the puncture site for 1 min. The needle tip was sealed with a rubber stopper to prevent gas from entering or exiting. Within an hour of collection, the samples were placed on a bed of crushed ice and promptly transported to the laboratory for analysis. Utilizing a blood gas analyzer (ST-200 CC, Blood Gas Analyzer®, Sensacore, India), the blood samples were analyzed for pH, partial pressure of oxygen ($_PO_2$), partial pressure of carbon dioxide ($_PCO_2$), and bicarbonate concentrations (HCO_3).

2.5. Acute phase protein measurements

Serum haptoglobin (Hp) concentration was assessed using an ELISA kit, following the protocol described by Hassanpour and Moghaddam (2023). Measurement of serum amyloid A (SAA) concentration was conducted using a commercially available ELISA kit, as per the method outlined by Alsemgeest et al. (1994). The serum fibrinogen (Fb) concentration was determined according to the procedure described by Campbell et al. (1981). Procalcitonin concentration was measured using a commercial ELISA kit designed for equine species (Horse Procalcitonin ELISA kit; My BioSource San Diego, USA).

2.6. Statistical analysis

The statistical analysis was performed using SPSS software (IBM, SPSS Statistics, Version 22, USA). The descriptive data are expressed as mean ± standard error (SE). The obtained results were analyzed using *t*-test, all data are listed as mean ± SE. The significance level was set at $P < 0.05$.

3. RESULTS

3.1.Clinical findings and signalment

Diseased foals were presented with signs of respiratory disease including increased body temperature, pulse, and respiratory rate, cough either on stimulation (37%) or spontaneous (63%), and on auscultation of the lung there was exaggerated vesicular sound (32%), wheezing (37%), pleuritic frictional sound (26%) and absence of lung sound (26%). Three foals were died; it showed severe respiratory distress, cyanotic mucous membrane, lowered body temperature and shallow breathing, they are presented for postmortem examination. The clinical findings and physical examination findings are listed in Table (1).

Table 1: Clinical signs and physical examination findings in apparently healthy and RDS-affected foals. Results were expressed as mean ± SE.

Clinical signs and physical examination findings	Control group (n = 7)	Diseased group (n = 19)	Sig
General systemic statement			
- Body temperature °C	37.8±0.13[b]	39.2±0.28[a]	0.04
- Pulse Rate/ minute	32±1.5[b]	60.4±4.3[a]	0.000
- Respiratory Rate/ minute	12±0.7[b]	35.4±4.02[a]	0.000
Coughing			
- Coughing up on stimulation	n = 0 (0 %)	n = 7 (37%)	
- Spontaneous coughing	n = 0 (0 %)	n = 12 (63%)	
Percussion of lung			
- Reduced resonance	n = 0 (0 %)	n = 15 (79%)	
- Increased resonance	n = 0 (0 %)	n = 4 (21%)	
Auscultation of the lungs			
- Exaggerated vesicular sound	n = 0 (0 %)	n = 6 (32%)	
- Wheezing sound	n = 0 (0 %)	n = 7 (37%)	
- Pleuritic frictional sounds	n = 0 (0 %)	n = 5 (26%)	
- Absence of lung sounds	n = 0 (0 %)	n = 5 (26%)	

3.2. Hematological examination

Hemoglobin, total protein, and albumin were significantly decreased ($P<0.05$) in diseased foals compared to clinically healthy foals. Diseased foals showed a significant increase in packed cell volume, erythrocytes, leucocytes, platelets, and neutrophils percent compared to clinically healthy foals. The results of the blood analysis are listed in Table (2).

Table 2: Blood analysis of apparently healthy and RDS-affected foals. Results were expressed as mean ± SE and were compared to the reference values of Constable et al. (2017).

Parameters	Control group (n = 7)	Diseased group (n = 19)	*P value*
Hb (g/dl)	12.74±0.25[a]	9.52±0.34[b]	0.000
PCV (%)	31.3±0.53[b]	37.32±0.48[a]	0.001
RBCs ($\times10^6$ cells/µL)	6.64±0.15[b]	8.36±0.28[a]	0.035
WBCs ($\times10^3$ cells/µL)	6.02±0.18[b]	17.05±0.42[a]	0.028
Neutrophils (%)	3.65±0.24[b]	13.28±0.18[a]	0.000
Platelets count(×103 cells/µL)	105.6±5.5[b]	267.4±12.46[a]	0.001
Total protein (g/L)	65.4±1.36[a]	52.6±1.07[b]	0.008
Albumin (g/L)	29.6±2.2[a]	18.84±0.44[b]	0.021

3.3. Blood gas analysis

Foals with respiratory distress syndrome showed a significant (P<0.05) decrease in pH, $_PO_2$, and base excess compared to clinically healthy foals (Table 3). While $_PCO_2$ and HCO_3 were significantly increased in diseased foals compared to clinically healthy foals.

Table 3: Blood gas analysis of apparently healthy and RDS-affected foals. Results were expressed as mean ± SE and were compared to the reference values of Constable et al. (2017).

Parameters	Control group (n = 7)	Diseased group (n = 19)	*P value*
pH	7.37±0.004[a]	7.23±0.008[b]	0.049
PCO_2 (mmHg)	35.92±0.61[b]	53.86±2.22[a]	0.036
PO_2 (mmHg)	66±0.71[a]	27.66±1.7[b]	0.048
HCO_3 (mmol/L)	27.52±0.58[b]	29.14±0.12[a]	0.000
BE (mM)	0.02±0.4[a]	-2.54±0.4[b]	0.005

pH: hydrogen ion concentration; PCO_2: Carbon dioxide pressure; PO_2: Oxygen pressure; HCO_3: Bicarbonate ; BE: base excess.

3.3. Acute phase proteins

Acute phase protein results are listed in Table (4). Serum amyloid A, Haptoglobin, Fibrinogen, and procalcitonin concentrations were significantly increased ($P < 0.05$) in foals suffered from respiratory distress syndrome compared to clinically healthy foals.

Table 4: Serum acute phase proteins of apparently healthy and RDS-affected foals. Results were expressed as mean ± SE and were compared to the reference values of Constable et al. (2017).

Parameters	Control group (n = 7)	Diseased group (n = 19)	Reference values
Serum Amyloid A (mg/l)	0.53±0.25 (0.00-1.5)[b]	279.8±134.7 (50-800)[a]	0-20 mg/l
Haptoglobin (mg/dl)	186±26.9 (100-250)[b]	991±69.36 (835-1200)[a]	
Fibrinogen (g/l)	161±13.8 (130-210)[b]	820±86 (600-1100)[a]	
Procalcitonin (ng/ml)	13.6±1.4 (10.12-18.28)[b]	183±3.7 (174.5-194.3)[a]	

Data represented as Mean ± SE. Superscript letters indicated significance difference between groups on P<0.05

3.5.Postmortem findings

Postmortem findings were obtained from foals that died before treatment due to severe illness. The serosanguinous foam was observed through the nostrils. Presence of serosanguinous fluid in the thoracic cavity with the presence of fibrin in abundant quantity, the lungs showed congestion and necrotic patches, with the presence of foam in the trachea and bronchi (Figures 1 and 2).

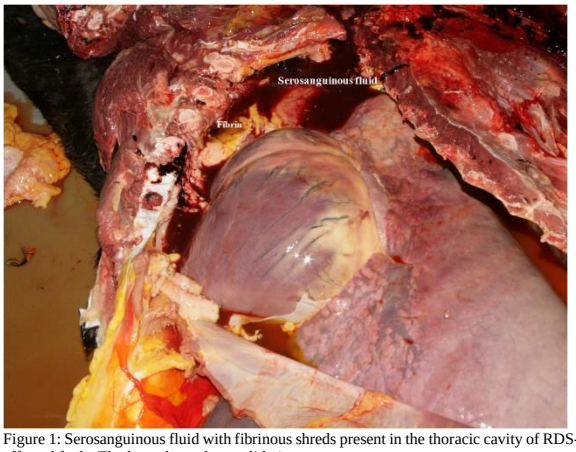

Figure 1: Serosanguinous fluid with fibrinous shreds present in the thoracic cavity of RDS-affected foals. The lung showed consolidation spots.

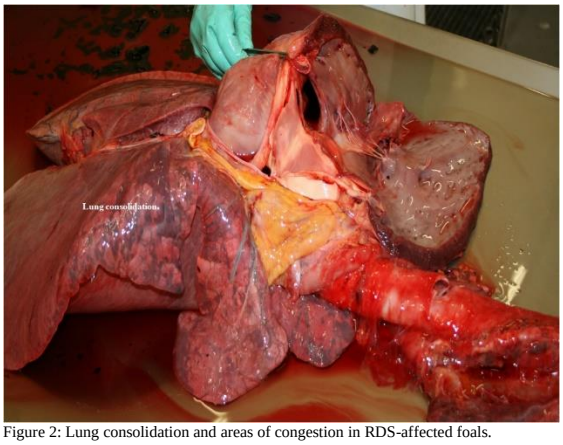

Figure 2: Lung consolidation and areas of congestion in RDS-affected foals.

4. DISCUSSION

One of the most common problems affecting horses and posing a threat to their health is respiratory distress syndrome. Coughing, nasal discharge, accelerated respiratory rate, hyperventilation, and wheezes in the lungs due to dyspnea were observed in the current study, indicating that bronchial and alveolar inflammation interferes with gas exchange and respiration. The absence of lung sound may be due to the accumulation of fluids in the bronchi and bronchioles. This was in agreement with previous studies by Giguère et al. (2004), Thomé et al. (2018) who recorded similar clinical signs in foals with pneumonia. In the current study, foals with respiratory distress syndrome showed elevated body temperatures, pulse rate, and respiratory rate indicating an acute stage of respiratory disease. According to previous research conducted by Thomé et al. (2018), foals with pneumonia tend to have fever exceeding 39 °C. Moreover, Johns (2013) stated that fever plays a significant role in diagnosing pneumonia in foals, particularly pneumonia caused by *R. equi*.

As a consequence of the pathological actions of microorganisms on the lungs, blood gas exchange and blood pH may be altered. There was agreement with other studies, that foals suffering from equine respiratory disease showed a significant increase in $_PCO_2$ and HCO_3 and a significant decrease in pH and $_PO_2$. As a result of a high respiratory frequency and aerobic metabolism, $_PCO_2$ and HCO_3 levels increase and $_PO_2$ levels decrease. An elevated leucocytic count might contribute to the decrease in $_PO_2$ level caused by oxygen consumption during metabolism; this was in agreement with previous studies (Kosch et al., 1984).

Haematological analysis revealed an increase in the leucocytic count, neutrophil percentage, hematocrit, and platelet counts in diseased foals compared to healthy foals. The increased platelet counts and neutrophilic leukocytosis in a foal with respiratory distress syndrome were closely associated with evidence of an infectious or inflammatory response in the lungs; this was in agreement with a previous study by Šoltésová et al. (2015). In addition, previous studies by Sellon et al. (1997) reported that hyperfibrinogenemia, leucocytosis, thrombocytosis, and anemia are symptoms of inflammatory or infectious diseases in foals. In addition, hypoproteinemia and hypoalbuminemia could be attributed to hepatic dysfunction as previously described by Arroyo et al. (2017).

Additionally, although *Rhodococcus equi* is most commonly known to harm the lungs, it can also damage other organs and joints. Therefore, in many instances, there is not only a local reaction but also a systemic inflammatory response (Barton et al., 2016).

Acute phase proteins have been proposed as sensitive and quick indicators of inflammatory processes in horses because they are blood proteins produced primarily by hepatocytes and a component of the innate immune system's acute phase response (Petersen et al., 2004), (Cray et al., 2009).

Albumin is a notable example of a negative APP, whereas positive APPs include fibrinogen, haptoglobin, and serum amyloid A. Positive APP levels in the serum/plasma rise in response to a triggering event (such as an infection or trauma) and fall as the individual recovers; the degree of the rise and the speed of the fall varies by species and individual APP (Petersen et al., 2004). In addition, procalcitonin has been demonstrated to be a sensitive marker for systemic inflammatory processes brought on by bacterial infection in the late 1990s, but not for other pathogenesis (Russwurm et al., 1999), (Reinhart et al., 2000), (Barton et al., 2016). In lab animals, dogs, horses, and human patients, PCT is released from numerous tissues and cell types in the body (Nocera et al., 2021).

In the current study, increased levels of plasma SAA, Hp, Fb, and PCT may be a result of severe lung tissue injury brought on by inflammation in horses, highlighting their function in host immunity. These findings were in agreement with studies by Stoneham et al. (2001), (Crisman et al., 2008). here, they suggested that a value of SAA over 200 mg/l was indicative of infection (Witkowska-Piłaszewicz et al., 2019). Stoneham et al. (2001) concluded that measuring SAA concentration is useful in diagnosing infectious diseases in equine neonates. The concentrations of SAA, the only significant positive APP in horses, are clinically undetectable in healthy animals but rapidly increase more than 10-fold during APR and rapidly decrease as the disease resolves (Crisman et al., 2008). While, plasma PCT concentration increases significantly within 3–6 hours, especially in response to bacterial infection and endotoxemia, and appears to be a marker for these conditions in early stages in human patients (Riedel, 2012). However, the horse's fibrinogen and haptoglobin, which are found in the serum and plasma of healthy animals, respond to stimuli more slowly and increase 1 to 10 times during the APR. It is suggested that plasma SAA as well as PCT concentrations are more precise indicators of infection in horses, similar to studies comparing SAA and PCT concentrations with those of other commonly used biomarkers of infection, such as WBC count and fibrinogen (Hultén and Demmers, 2002), (Barton et al., 2016), (Bonelli et al., 2018), (Nocera et al., 2021). On the other hand, 3 foals died in this study might be attributed to heart failure and respiratory failure due to difficulty in breathing and abnormal oxygenation of blood, necropsy findings consisted of serosanguinous fluid accompanied by consolidation; this was in agreement with a previous study by Oliveira et al. (2019).

5. CONCLUSIONS

According to the current study, it is concluded that tracking plasma SAA as well as PCT markers in horses with respiratory diseases can help with early disease detection, disease progression, and decision-making regarding biosecurity and isolation of diseased foals. In addition, the pulmonary function tests (pH, $_{P}O_2$, $_{P}CO_2$, and HCO_3) play an important role in the assessment of the lungs and respiration process in foals with respiratory distress syndrome.

CONFLICT OF INTEREST

The authors have indicated that they have no conflict of interest regarding the content of this article.

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