The Effect of Tryptophan-induced Pulmonary Injury on the Susceptibility to Experimental Infection with *Pasteurella multocida* in Young Nubian Goat kids

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Abstract

The effect of tryptophan – induced lung injury on the susceptibility to experimental *Pasteurella multocida* infection was investigated in young Nubian goat kids. The repeated administration of a total of 10 daily oral doses of L. tryptophan at a dose rate of 200mg/kg body weight resulted in the development of clinical signs of respiratory distress due to occurrence of acute pulmonary edema and emphysema in tryptophan treated goat kids. Also, the intra-tracheal inoculation of an infective dose of 1.0 ml of a virulent culture of *P. multocida* containing 1.0 X10^9 CFU/ml resulted in the onset of clinical signs of acute febrile respiratory disease in all experimental kids with the presence or absence of tryptophan pre-treatment. The disease was characterized by acute fibrinous or fibrinopurulent bronchopneumonia and pleurisy. However, an increased susceptibility to experimental infection with *P. multocida* was clearly observed in tryptophan pre-treated goat kids as reflected by the development of more severe clinical signs and death of infected animals. It is concluded that the amino acid L. tryptophan is pneumotoxic to young goat kids. Feeding with excessive amounts of green plants containing high levels of the compound will eventually increase animal susceptibility to natural field infection with *P. multocida*.

Key words: Tryptophan – pneumonic pasteurellosis - *Pasteurella multocida* - Nubian goats

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Introduction

Pasteurella multocida and *Mannheimia haemolytica* (formerly known as *Pasteurella haemolytica*) are the most important members of the Family *Pasteurellaceae* that cause serious diseases in various species of farm animals and poultry (Biberstein and Hirsh, 1999; Quinn *et al,* 2011). Both organisms have consistently been isolated from the tonsils, nasopharynx and other parts of the upper respiratory tract mucosa of sick animals and also from apparently healthy animals (Glimour *et al,* 1974; Frank and Smith, 1983; Adlam and Rutter, 1989; Al- Tarazi and Dangall, 1997). In fact, they are typical opportunistic pathogens that are capable of causing disease whenever the immune system of the animal is compromised (Frank, 1989; Brogden *et al*, 1998; Ackermann and Brogden, 2000, Zecchinon *et al,* 2005). For this reason, disease outbreaks caused by these organisms are essentially triggered by a sudden exposure to some kind of environmental or physiological stress with consequent drop in the immune status of the susceptible animal. Examples of stress factors associated with *P. multocida* and *M. haemolytica* infections include harsh weather (extremely high or low temperature and heavy rains), overcrowding, long distance transport or shipping, poor management, malnutrition or starvation,parasitism, concurrent viral, bacterial, mycotic and parasitic infections or chronic debilitating diseases (Brogden *et al,* 1998; Mohamed and Abdelsalam, 2008). Infection with either organism is usually characterized by a sudden onset of high fever, respiratory manifestations (pneumonia) or septicemia. The respiratory form of the disease has long been recognized by the name of shipping fever or pneumonic pasteurellosis which is characterized by the development of acute fibrinous or fibrinopurulent bronchopneumonia and pleurisy (Adlam and Rutter, 1989; Ackermann and Brogden, 2000; Zecchinon *et al*, 2005).

Tryptophan is a naturally occurring amino acid present in various types of fresh fodders and green plants. The substance is known to be associated with the development of an acute respiratory syndrome in cattle known as acute bovine pulmonary edema and emphysema (ABPEE). The disease is also known as acute or atypical interstitial pneumonia (AIP) or fog

fever (Lopez, 2007). The condition usually occurs after a sudden change to rapidly growing green pasture or succulent plants containing high levels of the amino acid tryptophan (Hammond *et al*, 1979; Doster, 2010). Clinical signs of acute respiratory distress with characteristic pathological lesions of atypical interstitial pneumonia were experimentally induced by a single or repeated oral doses of L-tryptophan in cattle, sheep and goats (Yokoyama, Carlson and Dickinson, 1975; Hammond, Huntington and Breeze, 1983; Hananeh and Ismail, 2018). The tryptophan induced pulmonary injury was suggested to be due to conversion of the amino acid into some active pneumotoxic metabolites including 3-methyl indole (3 MI), indole acetic acid and indole by microbial fermentation in the rumen (Hammond, Carlson and Breaze, 1980; Bray and Kirkland, 1990; Arnold and Lehmkuhler, 2015). However, the precise mechanism by which the indole derivatives of tryptophan can induce pulmonary damage is not fully understood but these metabolites were suggested to act directly by causing vascular leakage and disruption of the cellular membranes of type I pneumocytes due to their lipophilic properties (Hanafy and Bogan, 1980; Potchoiba, Carlson and Breeze, 1982).

Because of the fact that pneumonic pasteurellosis is a multifactorial disease which requires a predisposing stress factor, the present work was designed to determine the effect tryptophan-induced lung injury on the susceptibility of young Nubian goat kids to the experimental infection with *Pasteurella multocida.*

Materials and Methods

Tryptophan

L-tryptophan powder (Fluka Biochemka, Swizerland) was obtained from the Department of Biochemistry, Faculty of Veterinary Medicine, University of Khartoum.

Infective material

Lyophilized *Pasteurella multocida Type B* culture was obtained from the Department of Vaccine Production, Central Veterinary Research Laboratory, Soba, Khartoum.

Preparation of infective dose

The lyophilized culture was reconstituted in nutrient broth and incubated at 37^{O}C for 24hours. It was then inoculated onto brain-heart infusion agar plates and incubated at 37^{O}C for 24 h. Thereafter, the organism was harvested in phosphate buffered saline (PBS) and washed with PBS three times. 10 µL of the bacterial dilution in PBS were spread onto brain-heart infusion agar plates and incubated at 37ºC for 24- 48 hours. The growth was observed and the colony morphology was checked. The identity of the organism was confirmed according to Cowan and Steel's Manual for the Identification of Medical Bacteria (Barrow and Feltham, 2004). Plates with 30-300 colonies were counted and the dilution of the original stock was calculated. The exact number of bacteria was checked by direct plate viable count just before being inoculated into the experimental animals.

Experimental animals

Sixteen 3 – 4 month old male Nubian goat kids were purchased from a local livestock market West Omdurman Town (Gondohar Area) . They were housed in clean and disinfected pens and fed *ad libitum* with green lucerne (*Medicago sativa*) and sorghum hay with free access to drinking water. The animals were allowed a two-week period of adaptation during which they received prophylactic doses of antibiotic and anthelmithic drugs. Their body temperature and general health condition were repeatedly checked before experiments commenced.

Experimental design

The experimental goat kids were allotted into four separate equal groups and treated according to the following protocol:

Group I goat kids (Nos.1, 2, 3&4) were each drenched with repeated daily doses of L-tryptophan (200mg / kg b.w.) for 10 days before being slaughtered on day 11 for examination of tryptophan induced lung injury.

Group II goat kids (Nos. 5, 6, 7 &8) were each inoculated with an infective dose of 1.0 ml *P. multocida* culture containing 1.0 X10^{9} CFU/ml, administered by the intra-tracheal route.

Group III goat kids (No. 9, 10, 11&12) were first given repeated daily doses of L- tryptophan (200mg / kg b.w.) for 10 days before being challenged on day 11 with the same amount of the

infective dose of *P.multocida* given to Group I goat kids (1.0 ml of diluted culture containing 1.0 X10^9 CFU/ml).

Group IV goat kids (Nos13, 14, 15 &16) were kept as undosed /uninfected controls.

Clinical and pathological methods

Experimental goat kids were thoroughly observed for abnormal clinical deviations immediately after the administration of tryptophan or inoculation with the infective material with and without pretreatment with tryptophan. A special attention was directed towards the appearance of respiratory manifestations such as dyspnea, irregular respiration, nasal and ocular discharges, sneezing, snoring or cough. Detailed postmortem examination was carried out on group 1 goat kids which received a total of 10 daily oral doses of tryptophan and sacrificed on day 11 and on other goat kids which died as a result of. *P. multocida* infection with or without tryptophan pre-treatment. Representative tissue specimens collected from the lung, liver, kidney, heart and brain were immediately fixed in 10% buffered formalin solution for histopathological processing, sectioning and staining with haematoxylin and eosin (H&E) as described by Bancroft and Gamble (2007).

Results

Clinical observations

Group I goat kids which received a total of 10 daily doses L. tryptophan at a dose rate of 200mg/kg b.w. initially suffered difficult breathing, irregular respiration and appearance of mucous discharges from the nasal openings after each dose. They further showed prominent clinical signs of respiratory distress manifested by labored breathing, irregular respiration and intermittent cough throughout the course of tryptophan pretreatment. Nonspecific clinical signs including dullness, restlessness and reduced appetite were also observed in all goat kids given daily oral doses of tryptophan for ten days.

Group II goat kids which were inoculated with an infective dose of *P.multocida* developed mild to moderate signs of respiratory distress and intermittent cough a few hours following inoculation. Thereafter the animal became depressed, restless and had reduced appetite. They further became

dull, inactive and developed fever, increased respiration, moist cough and nasal discharges. One goat kid (No.5) showed more severe clinical signs and became recumbent, off food and died 48 hours post infection. The remaining goat kids continued to show clinical signs of respiratory distress, intermittent cough, reduced appetite and dullness. However, they started to show gradual recovery by the end of the second week post infection and appeared clinically normal at the end of the observation period (21 days).

Group III goat kids which were first pretreated with tryptophan for 10 days before being challenged with *P.multocida* showed persistent signs of respiratory distress throughout the course of L. tryptophan pretreatment. However, the respiratory distress was considerably exaggerated a few hours after challenge with *P.multocida*. The animals then developed severe respiratory signs including labored breathing, increased respiration, intermittent cough and nasal discharges. They appeared dull and had fever and reduced appetite. Further on, they became very weak, depressed and off food. Three animals died 48 hours post infection after a short period of recumbency. However, one animal survived infection and gradually recovered as from the second week.

Control goat kids (Group IV) remained apparently healthy and did not exhibit any abnormal clinical changes throughout the period of observation (21 days).

Pathological findings

Gross Lesions

Group I goat kids which received repeated daily oral doses of L. tryptophan for up to 10 days showed consistent gross lesions of diffuse pulmonary edema and emphysema. The lungs were considerably inflated and didn't collapse when the thorax was opened. They appeared moist, edematous and shiny with prominent rib imprints on the lung surface (Fig.1). Large amount of frothy fluid was oozing from the trachea (Fig 2). Straw-colored fluid was also detected in the thoracic cavity (hydrothorax). The heart was flabby with increased amounts of pericardial fluid. It was pale in color, thin walled and with depleted coronary fat.

Group II goat kid (No.5) which was intra-tracheally inoculated with *P.multocida* without tryptophan pretreatment and died 48 hours post infection showed gross evidence of acute

pulmonary congestion, diffuse edema and early signs of pneumonia involving the entire apical lobe (Fig 3). Excessive amount of straw- colored fluid was found in the thoracic cavity. Fibrinous adhesions of ventral parts of the apical lobe with the parietal pleura were observed. The heart was flabby with thin walls and the pericardium contained excessive amounts of straw-colored fluid.

Group III goat kids which were first pretreated with tryptophan for 10 days and then challenged with *P.multocida* showed similar but more severe gross pulmonary lesions as those observed in Group I goat kid. The lungs were acutely congested, edematous and with multiple fibrinous adhesions of the visceral pleura with the ventral parts of the consolidated apical lobe. Petechial and ecchymotic hemorrhages were observed in the serous membranes. The heart was flabby and the pericardial sac was considerably thickened and filled with increased amount of serofibrinous fluid (Fig .4). Large amount of turbid fluid containing fibrinous strands was also present in the abdominal cavity.

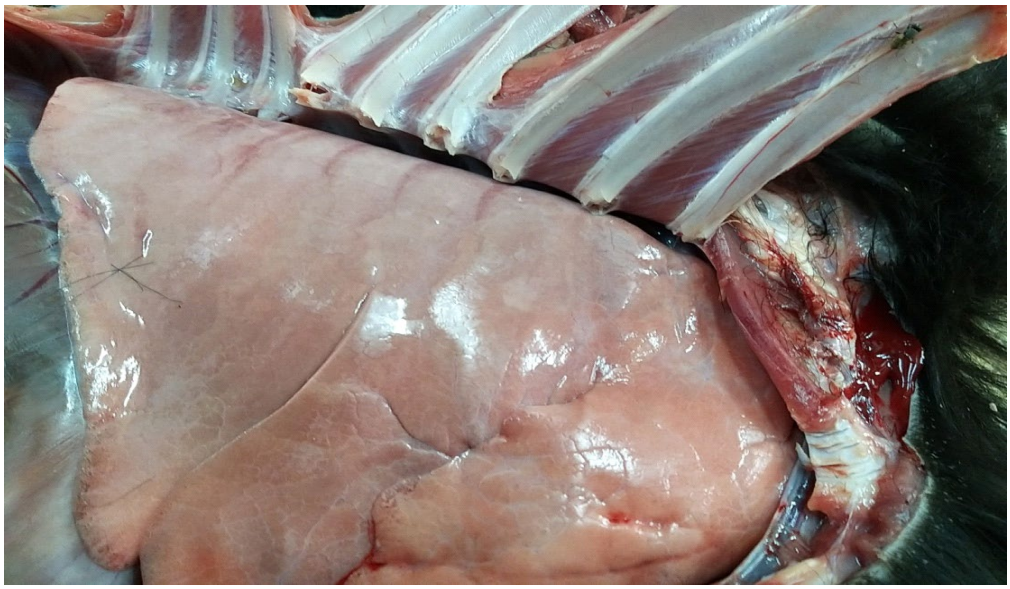

Fig.1: Lung of L. tryptophan treated goat kid (group I) showing edema, emphysema and prominent rib imprints on the lung surface.

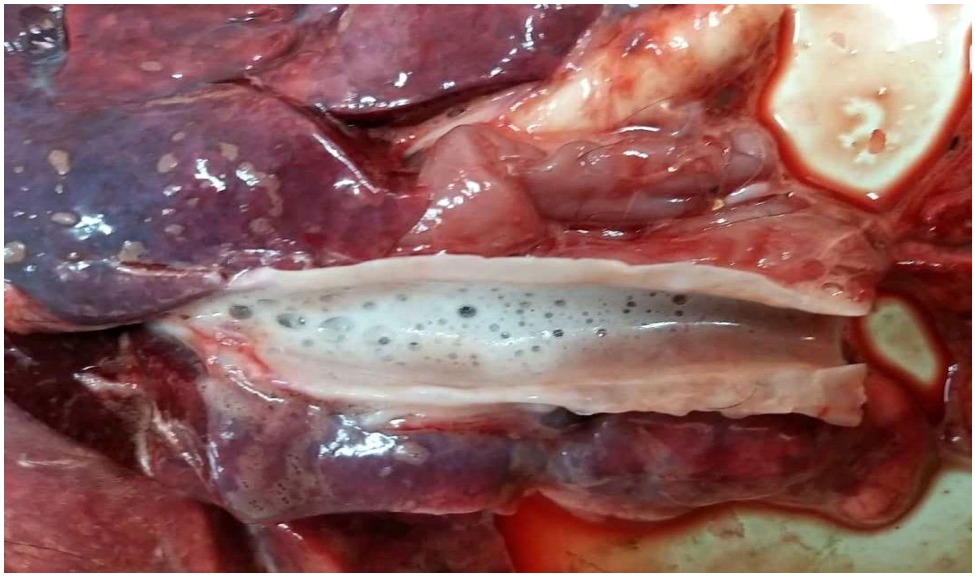

Fig 2: Lung of the same goat kid showing acute congestion, edema and frothy fluid oozing from the trachea.

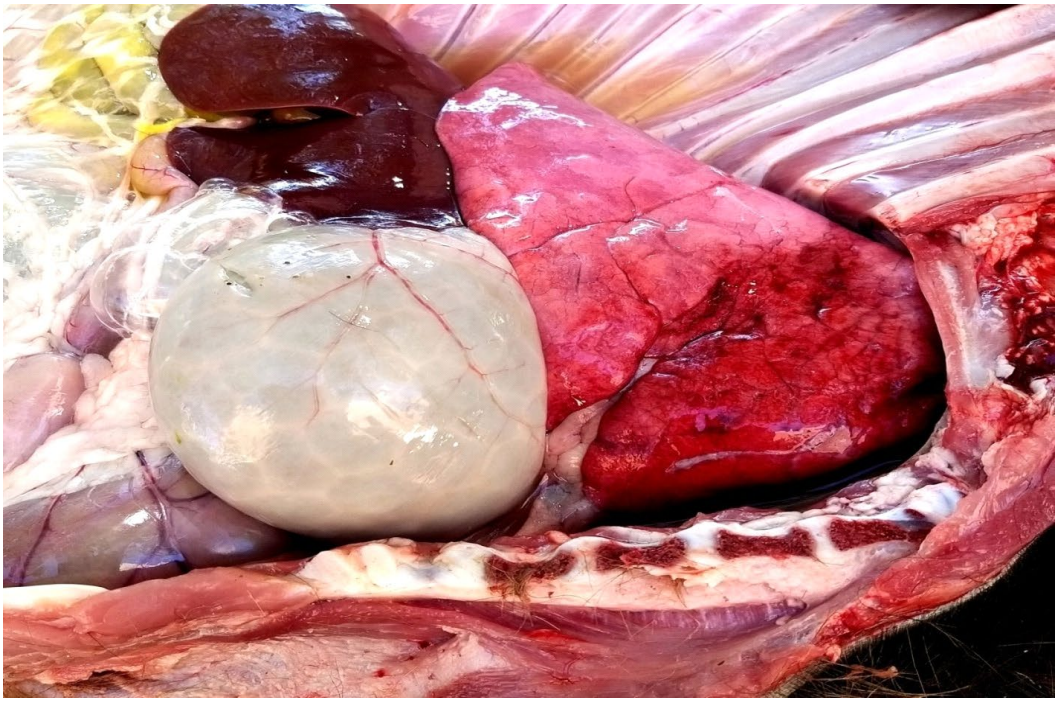

Fig 3: Thoracic and abdominal view of *P. multocida* infected goat kid (Group II) showing early pneumonic changes involving the entire apical lobe.

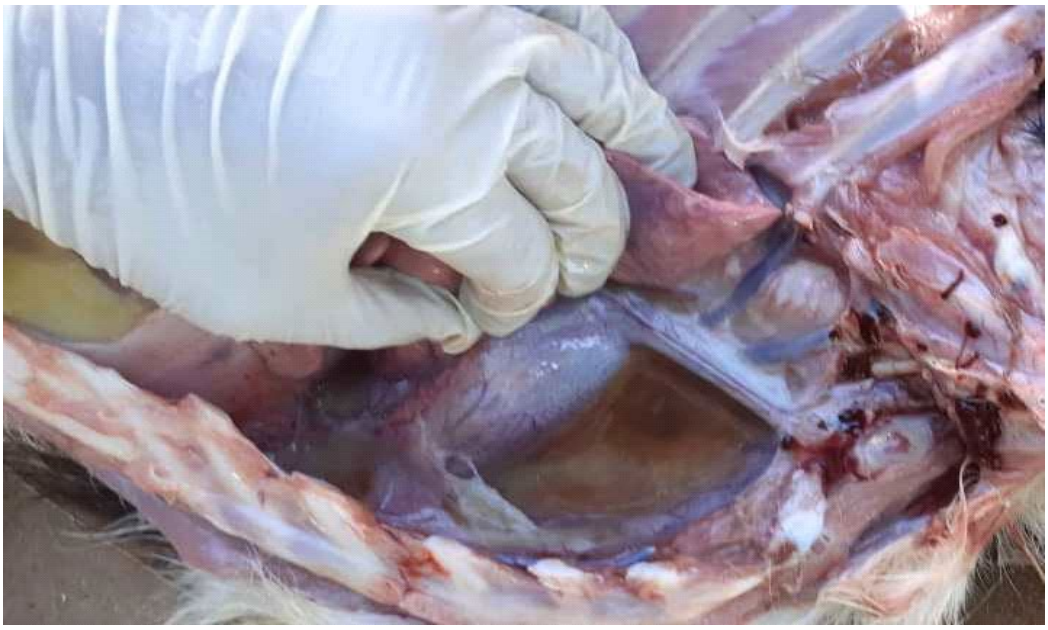

Fig: 4. Thoracic cavity of *P. multocida* infected goat kid after pretreatment with tryptophan (group III) showing hydrothorax, hydropericardium and thickening of the pericardial sac.

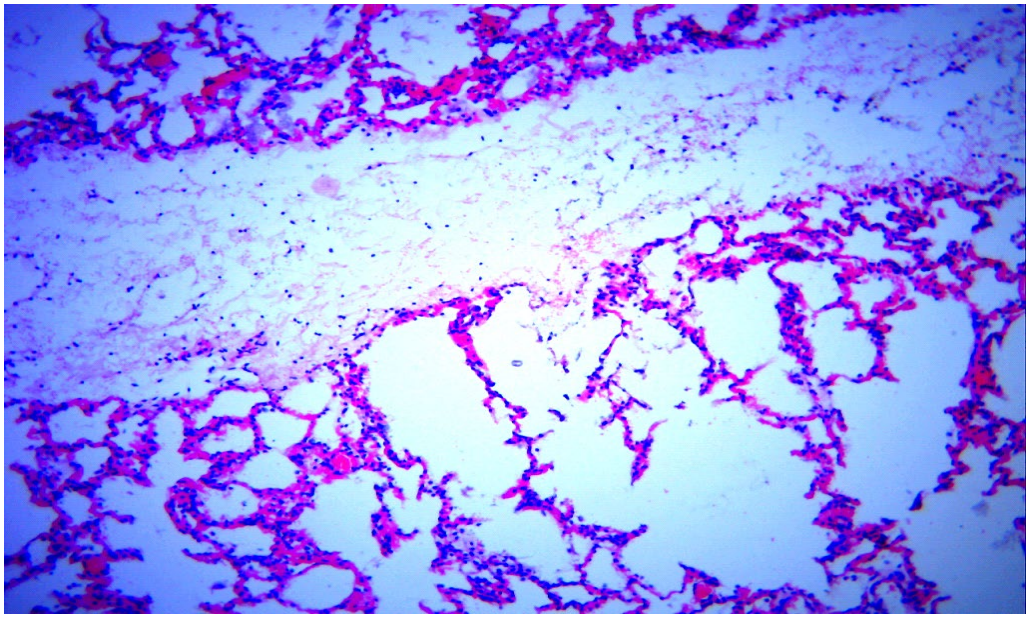

Fig. 5: Lung of tryptophan treated goat kid (Gruop1) showing interlobular edema and multifocal alveolar emphysema (H&E X 100).

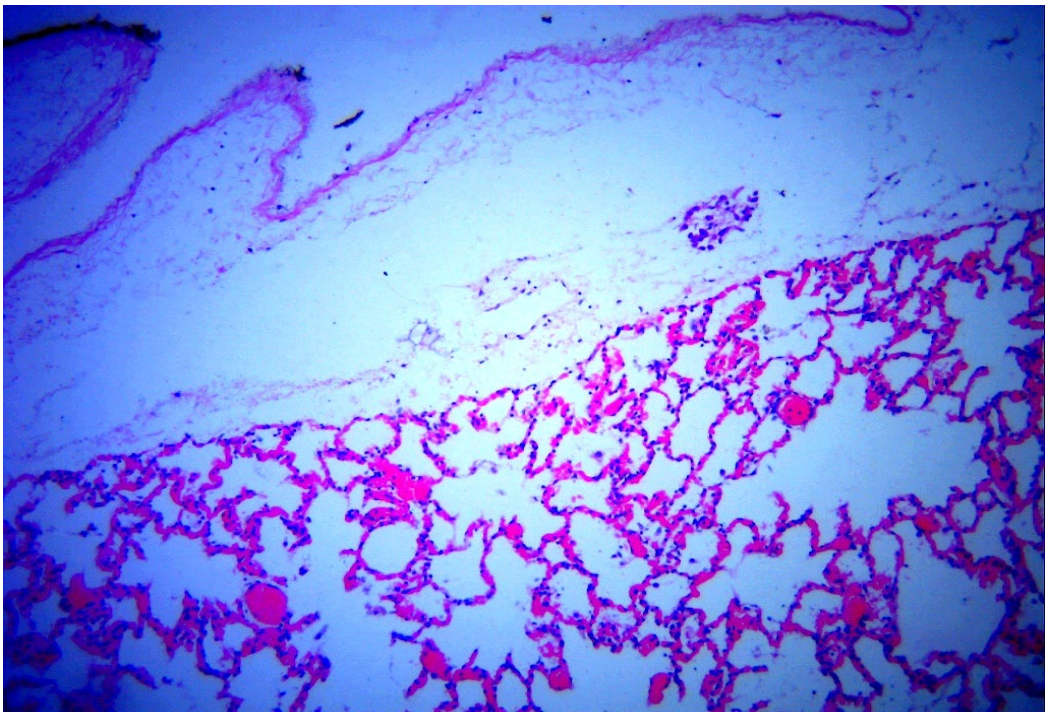

Fig 6: Lung of the same goat kid described above showing edema fluid in the sub-plural space (H&E X 100).

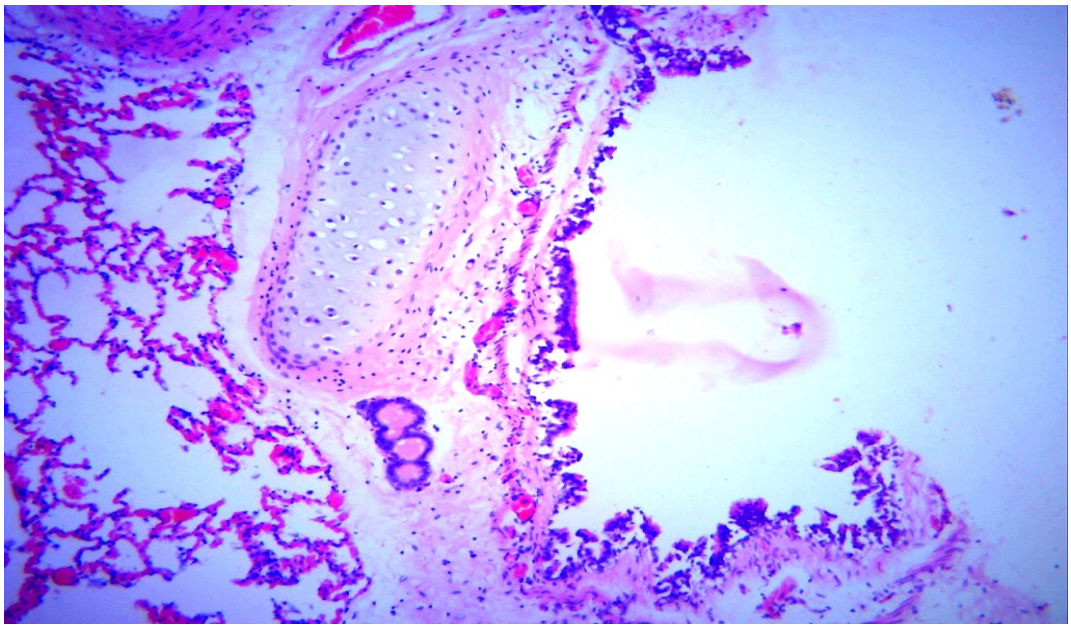

Fig.7: Lung of the same goat kid described above showing destruction, necrosis and desquamation of the bronchial epithelium (H&E X 100).

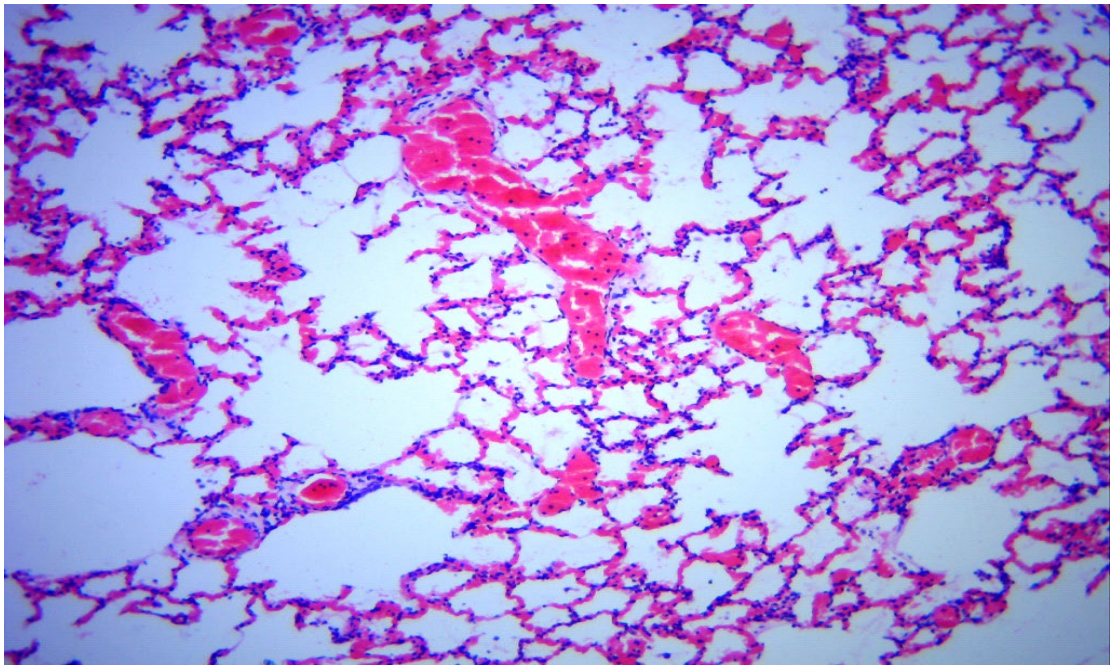

Fig. 8: Lung of *P. multocida* infected goat kid (group II) showing acute congestion of blood vessels and capillaries (H&EX100).

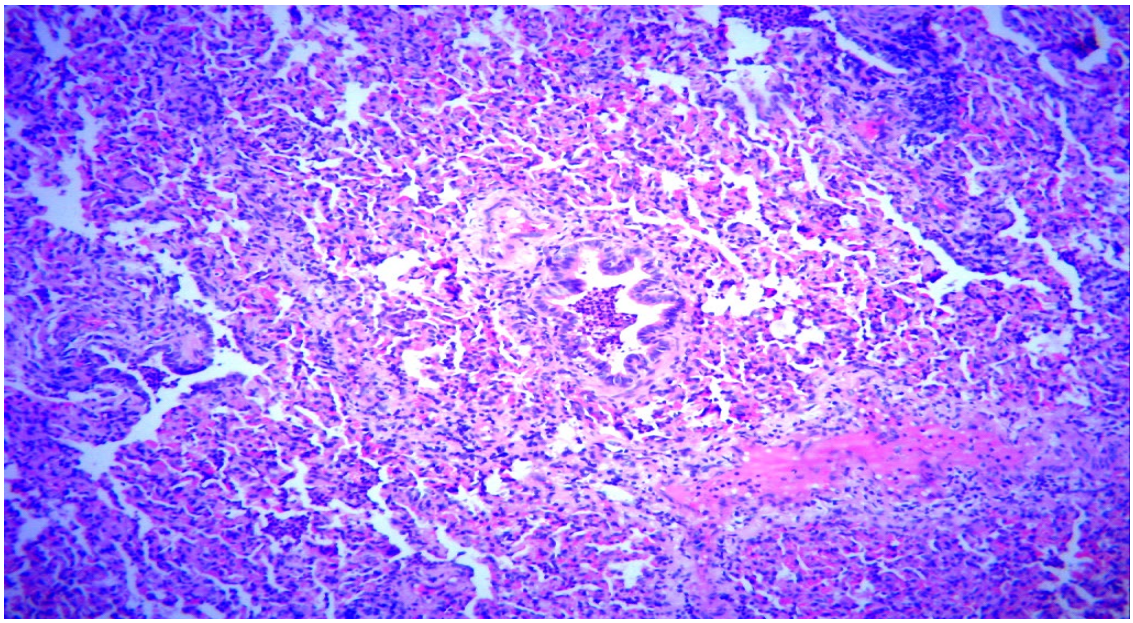

Fig. 9: Lung of *P. multocida* infected goat kid after tryptophan pretreatment (Group III) showing acute fibrinopurulent bronchopneumonia with destruction and collapse of alveoli (H&E X100).

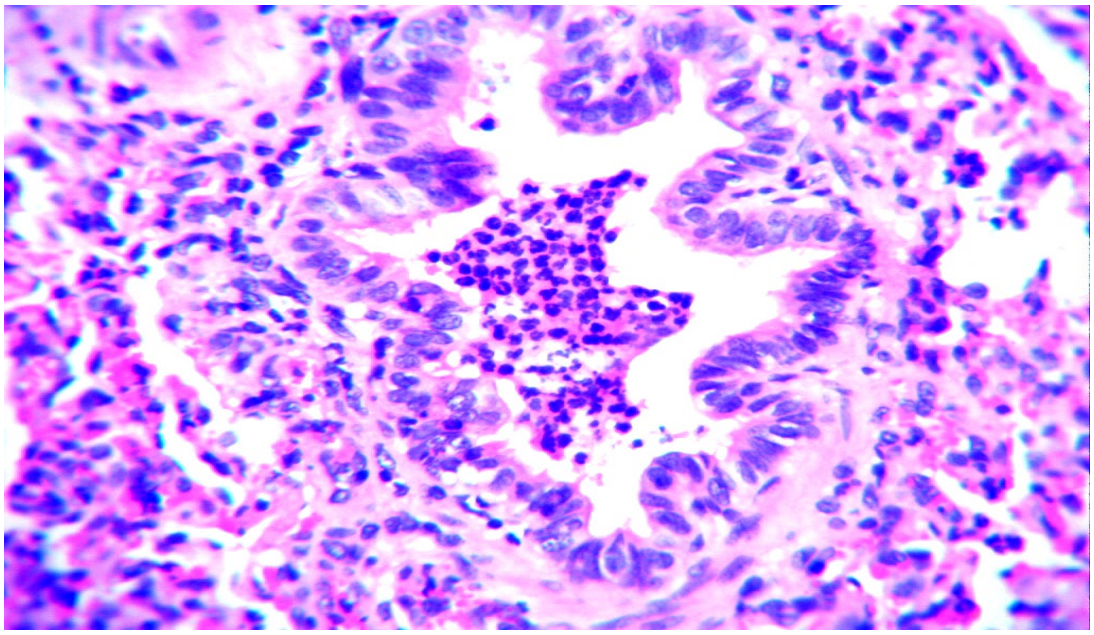

Fig. 10: Higher magnification of the previous figure showing infiltration of neutrophils in the lumen of a bronchiole (H&E X400).

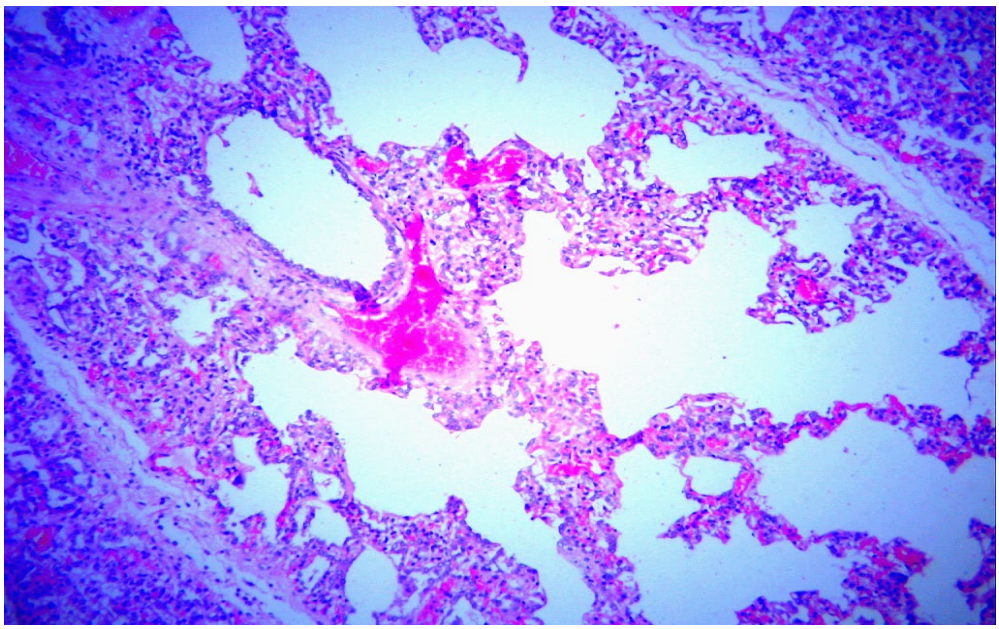

Fig. 11: Lung of the same goat kid (group III) showing thickening of the alveolar wall due to proliferation of pneumocytes type II and infiltration of mononuclear cells. (H&E X 100).

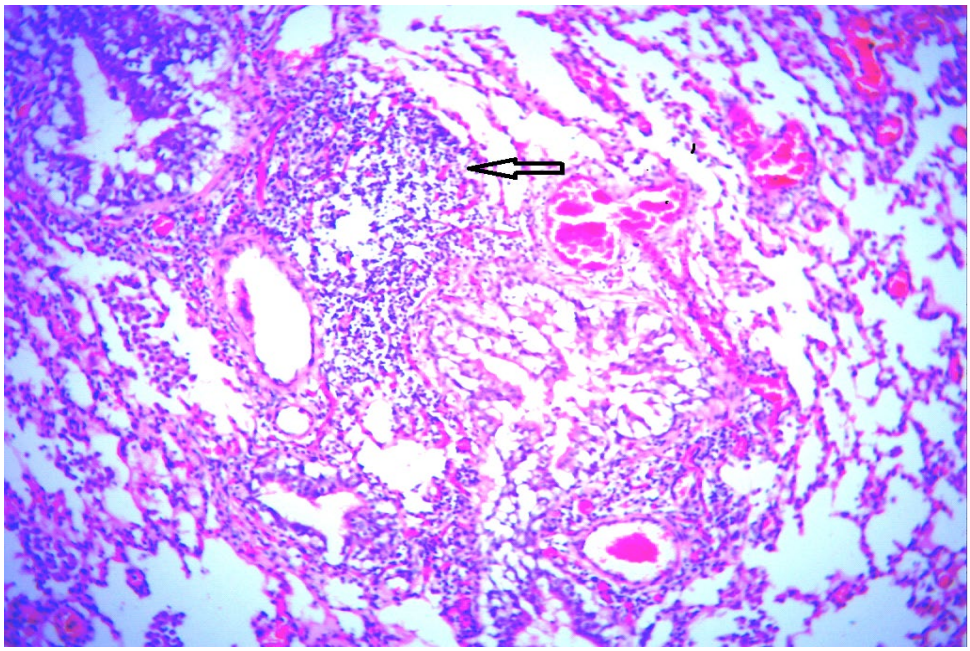

Fig. 12: Lung of *P. multocida* infected goat kid after tryptophan pretreatment (group III) showing acute bronchiolitis and hyperplasia of the bronchial associated lymphoid tissue (BALT) forming discrete lymphoid nodules (arrow) (H&E X 100).

Histopathological findings

Group I goat kids which received 10 daily repeated oral doses of L. tryptophan showed consistent histopathological changes in the lung tissue dominated by multifocal alveolar emphysema and interlobular edema (Fig 5). Some of severely distended alveoli were ruptured forming very large alveoli (giant alveoli). Also, there was widespread and severe congestion of blood vessels and alveolar capillaries throughout the pulmonary parenchyma. In addition, there was remarkable thickening of the visceral pleura (lung serosa) due to accumulation of edema fluid in the sub-pleural space (Fig 6). The intra-pulmonary bronchi and bronchioles showed destruction, necrosis and desquamation of the bronchial epithelium (Fig. 7). In addition, there was thickening of the alveolar wall due to proliferation of pneumocytes type II and infiltration of mononuclear cells including macrophages and lymphocytes.

Group II goat (No.5) which was intra-tracheally inoculated with *P.multocida* without tryptophan pretreatment showed prominent histopathological alterations of early stages of acute

bronchopneumonia. There were severe vascular changes dominated by diffuse congestion (active hyperemia) involving sizable portions of the lung parenchyma (Fig.8). The capillaries of the alveolar walls were greatly distended with large amounts of erythrocytes. Intra-alveolar hemorrhages were also observed as indicated by the presence of large amounts of erythrocytes inside alveoli.

Group III goat kids which were first pretreated with a total of 10 daily repeated oral doses of L-Tryptophan before being challenged by *P. haemolytica* showed more severe pulmonary histopathological changes The lesions were more severe than those already seen in group II goat kid which was infected with *P. multocida* without tryptophan pretreatment.. The lung showed microscopic evidence of acute fibrinopurulent bronchopneumonia characterize by diffuse infiltration of neutrophils and other inflammatory cells with massive destruction of alveoli throughout the lung parenchyma (Fig. 9). Intrapulmonary bronchi and bronchioles were also infiltrated with neutrophils and fibrinopurulent exudate (Fig. 10). The adjacent areas of the pneumonic portion of the lung showed prominent interstitial changes comprising alveolar emphysema, interlobular edema and thickening of the alveolar wall due to hyperplasia of type II pneumocytes, deposition of fibrin and infiltration of mononuclear cells on the alveolar wall (Fig.11). Other areas of the lung tissue showed peribronchial infiltration of lymphocytes and hyperplasia of bronchial associated lymphoid tissue (BALT) forming discrete lymphoid nodules (Fig. 12). Necrotizing bronchitis, bronchiectasis, and venous thrombosis were also observed in the lung tissue of goat kids pretreated with tryptophan before being challenged with *P. multocida*.

Discussion

The results of the present work showed that the repeated daily oral administration of L. tryptophan at a dose level of 200 mg/kg body weight for ten days resulted in the development of clinical features of acute respiratory distress in young Nubian goat kids The most prominent signs included labored breathing, increased respiration, irregular breathing, dyspnea and nasal discharges. The tryptophan induced clinical signs of acute respiratory distress observed in experimental goat kids in the present study were similar to those previously reported in adult cattle and goats receiving a single or repeated oral or intra-ruminal doses of L. tryptophan (Carlson, Dyer and Johnson 1968 ;.Schiffer, Jyasekara and Mills, 1974, Bradley and

Carlson,1980). The gross and microscopic lesions in tryptophan treated kids were mainly dominated by diffuse pulmonary edema and emphysema. The lungs were considerably inflated and pale in color. The trachea contained frothy fluid and large amounts of straw-colored fluid were frequently detected in the thoracic cavity and pericardial sac. Microscopic examination of affected lungs revealed the presence of diffuse interstitial edema, multifocal alveolar emphysema and hyperplasia of alveolar lining epithelium and thickening of alveolar septa. The tryptophan induced pulmonary lesions in experimental goat kids observed in the present study were similar to those previously described in adult cattle and goats given a single or repeated oral or intraluminal doses of L tryptophan (Dickinson, Spencer, and Gorham , 1967; Carlson, Dyer and Johnson, 1968; Schiffer, Jyasekara and Mills, 1974; Hammond, Carlson and Breeze, 1980). These lesions were also similar to those commonly observed in naturally occurring outbreaks of acute pulmonary edema and emphysema (APEE) or fog fever in adult cattle (Pirie *et al*, 1974 ; Kerr and Linnabary.1988; Costa *et al* 2018, Huang *et al*, 1977).

In the present work, the intra-tracheal inoculation of goat kids with a virulent culture of *P.multocida* resulted in the development of clinical signs of an acute febrile respiratory disease. All experimentally infected animals became dull, depressed and had reduced appetite. The animal showed high fever, labored breathing, increased respiration, intermittent cough and nasal discharges. The clinical signs observed in the experimentally infected goat kids in the present work were similar to those previously described for experimental and naturally occurring disease of pneumonic pasteurellosis caused by *P.multocida* or *M. haemolytica* in young calves (Dowling *et al*, 2002 ; Dabo, Taylor and Confer, 2007) sheep (Brogden, Lehmkuhland and Cutlip 1998; Odugbo, *et al*, 2006) and goats (Zamri-Saad *et al,* 1996; Shafarin *et al*, 2009).

The gross lesions observed in *P. multocida* experimentally infected goat kids with or without tryptophan pretreatment included acute pulmonary congestion, edema and bilateral pneumonic consolidation of the apical lobes of affected lungs. The histopathological alterations in affected lungs were dominated fibrinous or fibrinopurulent bronchopneumonia as indicated by severe vascular changes comprising diffuse congestion, hemorrhage and thrombosis. The alveoli, intrapulmonary bronchi and bronchioles were filled with fibrinous exudate and inflammatory cells mainly neutrophils. The above – mentioned gross and histopathological changes were consistently observed in natural and experimental cases of pneumonic pasteurellosis in cattle,

sheep and goats (Gibbs *et al,* 1984; Panciera and Corstvet, 1984; Gourlay, Thomas and Wyld, 1989; Vestweber *et al*, 1990; Zamri-Saad *et al*, 1996l; Sadeghian *et al*, 2011).

The results of the present experiment also showed that the susceptibility of the young Nubian goat kids to the experimental infection with *P. multocida* was apparently increased as the result of the daily administration of repeated oral doses of L. tryptophan. The increased susceptibility of the goat kids to the experimental infection with *P. multocida* was clearly evident by the development of more severe clinical signs and death of tryptophan pretreated animals. An increased susceptibility to the experimental infection with *P. haemolytica* was previously observed with concurrent infection with BRSV in young lambs (Al-Darraji *et al*, 1982; Trigo *et al,* 1984; Sharma and Woldehiwet, 1990). Susceptibility to the experimental infection with *P. haemolytica* was also increased in lambs inoculated with adenovirus (Davis *et al*, 1982). The same results were obtained in goats previously inoculated with caprine herpesvirus before bacterial challenge (Buddle *et al,* 1990). Primary infection of the lower respiratory tract with *Mycoplasma ovipneumoniae* was also found to increase the susceptibility of sheep to secondary infection with *P. haemolytica* (Brogden et al., 1998). The increased susceptibility of tryptophan – pretreated goat kids to the experimental infection with P. *multocida* in the present study was probably due to the pre-existing pulmonary injury produced by the repeated administration of the compound. The results therefore provides a circumstantial evidence that the sudden change to fresh pasture with green grass containing high levels of tryptophan may well act as a pre-disposing factor for field outbreaks of pneumonic pasteurellosis in susceptible animals. It is concluded that the amino acid L. tryptophan is pneumotoxic to young goat kids. Feeding with large amounts of green plants with high levels of the compound will eventually increase animal susceptibility to field infection with *P. multocida.*

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Compliance with ethical standards

All procedures performed in the present investigation were in accordance with the ethical standards of the international and national guidelines for the care and use of animals.

Conflict of interest

The authors declare that they have no conflict of interest.

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