

NEW INSIGHT IN THE MANAGEMENT OF ACUTE BOVINE RESPIRATORY DISEASES

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1. Introduction

Acute bovine respiratory diseases (ABRD) are the most important cause of sanitary economic losses in cattle. These problems are increasing despite the use of preventive and therapeutic agents. This could be due to several factors like increase of the population density in the cattle units, increase of the virulence of the pathogens, increase of air pollution, etc ... Another explanation could be that, in the past, bovine respiratory diseases have been analysed at a pathological but not functional level. In the light of new information on bovine pulmonary function in health and disease, it appears that, before the occurrence of irreversible and of course untreatable lung damages, there are some reversible dysfunctions at the level of pulmonary ventilation, perfusion or gas diffusion. An early and appropriate correction of these dysfunctions is of a critical importance in order to decrease the rate of mortality and chronic pneumonia.

The purpose of this paper is to analyse the peculiarities of the bovine pulmonary physiology and pathophysiology in order to try to improve the efficiency of the treatment of ABRD.

The prevention of ABRD, although highly important, is not analysed in this paper.

2. Theoretical studies

Measurement of the pulmonary function is necessary not only for the understanding of the bovine physiological and pathophysiological peculiarities but also for the study of the efficacy of therapeutical agents.

Information about the pulmonary function may be obtained by the measurement of some parameters of the mechanics of breathing. For example, the measure of the airway resistance, the dynamic compliance and the viscous work of breathing gives us information about the airway's permeability, the lung's elastic properties and the energetic cost of breathing respectively. On the other hand, the measure of arterial blood gases, i.e. PaO₂ and PaCO₂, gives us information about the ability of the lungs to meet the gas exchange requirements of the body.

3. Technical studies

Pulmonary function tests have been specially adapted for unsexed cattle both in physiological and pathological conditions. Some techniques, i.e. the pneumotachograph-oesophageal balloon one (1) and the forced oscillation one (2) must be used in laboratory conditions.

Some others, like the monofrequency forced oscillation method (3) have been specially developed for field studies. This last technique is indeed a simple, portable, reproducible, fast and accurate method for analysing the resistive and elastic properties of the bovine respiratory system under field conditions.

4. Physiological studies

Many factors may explain the peculiarities of the bovine pulmonary function, when compared to common mammals.

Their low alveolar surface area and their lower pulmonary capillaries/alveolar section are responsible of a higher basal ventilatory activity and lower ventilatory reserves (4).

The high anatomical compartmentalization of the bovine lungs is responsible of their lack of collateral ventilation which may induce a less appropriate ventilation to perfusion adequation (5).

The high hypoxic vasoconstriction can be responsible for a pulmonary

hypertension which can enhance the occurrence of oedema (6)

Their higher airway resistance and lung elastance are responsible for an increase in their viscous work of breathing and therefore in their energetical cost of breathing (7).

Concerning the control of breathing, their ventilatory response to hypercapnia and hypoxemia is lower, which may disturb gas exchange (8).

There is an exponential relation between arterial oxygen tension and the somatic growth; therefore the maximal gas exchange efficiency is not reached before one year of age in cattle (9).

The fact that cattle are ruminant has also some respiratory consequences. Firstly, 50 % of the ruminal eructated gases are eliminated via the airways and the alveoli. Therefore the occurrence of toxic gases in the rumen may induce lung damages and disturb gas exchanges (10). Secondly, the rumen mass influence the transdiaphragmatic pressure. Therefore an increase in the rumen pressure may anticipate the occurrence of the inspiratory muscles fatigue which can be responsible for a fatal ventilatory failure (11).

The breed is also of importance as regard to the ventilatory capacities. Indeed, the ratio lung mass/muscle mass is significantly higher in dairy than in beef cattle which is responsible in these last ones for their lower ability to meet the gas exchange requirements in some pathological conditions (12).

All these factors explain why cattle, and mainly beef ones, are disadvantaged for their pulmonary function and their sensitivity to severe respiratory diseases. Young animals are more concerned by these problems because of the functional immaturity of their respiratory system before one year of age.

5. Pathophysiological studies

Common ABRD have been analysed at a functional point of view, i.e. IBR, Shipping Fever, RSV pneumonia, ABRD due to 3MI, organophosphate poisoning, necrotic laryngitis, etc ... (13). Following these studies, new hypothesis have been developed in order to try to explain how cattle react to the aggression of their respiratory system.

When the pulmonary aggression (i.e. by biological, chemical or physical agents) is moderate, the organism will react by a moderate inflammation directed against the aggressor. The undesirable effects of this weak lung inflammation will be reduced by negative feed-back mechanisms induced by the organism, i.e., stimulation of respiratory centers, increase of muco-ciliar and alveolar clearance, increase of cardiac function and surfactant production, etc In these conditions, a spontaneous recovery may be observed.

However, when the lung aggression is too severe, the subsequent heavy inflammation will be able to also damage the lungs. Indeed the inflammatory process, via the release of endotoxin lipopolysaccharide, complement activation, release of C5 peptide and activation of alveolar neutrophils and macrophages, will bring to the lungs a lot of very powerful substances (14). Some of these (i.e. arachidonate metabolites, platelet activating factors, autacoides like histamine and serotonin, cytokines like interleukines and tumor necrosis factor, etc ...) are able to induce severe dysfunctions like bronchoconstriction, pulmonary hypertension, capillary leakage, hypersecretion and decrease of airway clearance, etc ... which will be responsible for poor gas exchange in the lungs. These resulting mechanical disorders, associated with the products issued from the activation of the neutrophils, i.e. oxygen radicals and proteases, may be responsible for the occurrence of lung damages, i.e. limited cells injuries up to diffuse emphysema. This hypothesis of a non exclusive but predominant role of the mechanical disorders in ABRD is reinforced by a recent publication which demonstrated that ABRD in beef cattle can be successfully treated by the use of bronchodilators without any antiinflammatory drugs (15).

In these dramatic conditions, the organism will react in an inappropriate way by positive feed back mechanisms (i.e. metabolic acidosis, inappropriate vasoconstriction, respiratory muscles fatigue, etc ...), which will induce a deterioration instead of an improvement of the clinical status. The resulting

vicious circles will be responsible for a fatal evolution if an appropriate treatment is not promptly used.

6. Pharmacological studies

In agreement with the above considerations, the therapeutical strategies of ABRD could include 3 ways, i.e. suppression of the aetiological agents, modulation of the lung inflammation and correction of the mechanical disorders, taking into account the efficacy, innocuity and lack of residues of the used drugs.

This optimal treatment should improve the (appropriate) negative feed-back mechanics and inhibit the (unappropriate) positive ones.

6.1. Suppression of the aetiological agents

Most of the ABRD are due to a multifactorial aetiology where virus and bacteria play an important role.

Antiviral agents like ribavirine have been showed to be active in vitro against the RS virus (16). However, the efficacy and safety of these drugs have not yet been demonstrated in infected calves (17). Inhalation of these drugs could maybe increase their efficacy and innocuity (18).

Anti-microbial treatments are needed in most severe ABRD because of primary or secondary involvement of bacteria and/or mycoplasma. The respect of all the golden rules of antibiotherapy is of course an important condition of efficacy. However, the importance of antibiotherapy must not be overestimated. Indeed many antibiotics have been recently showed to be highly active in vitro and in vivo against pulmonary pathogens (19-23). The remaining uncurrred patients must not be systematically due to a lack of efficacy of the anti-bacterial drugs. Therefore they seem not to be the major limiting factor of any further improvement in the management of ABRD.

6.2. Modulation of the lung inflammation

As mentioned earlier in this paper, the inflammation process in the pneumonic lung involves many types of mediators with complex and multiple interactions. Some of these mediators have beneficial effects. Some others must be inhibited when they disturb the gas exchange processes in the lungs. Several strategies may therefore be recommended alone or in association.

6.2.1. Inhibitors of the arachidonate metabolites

Prostaglandins (i.e. PGD₂, PGF₂α), thromboxanes (TXA₂) and leukotrienes (LTC₄, LTD₄, LTE₄) can induced severe pulmonary dysfunctions. Their global inhibition by antiinflammatory steroidal drugs, although very potent, seems not to be recommended during infectious diseases because of their side effects on the defense mechanisms. The use of more specific inhibitors like antiprostaglandins (24), antithromboxanes (25) and anti-leukotrienes (26) should be more appropriate in the treatment of ABRD.

6.2.2. Inhibitors of autocoïdes

Some autocoïdes like histamine are able to disturb the bovine pulmonary function during experimental administration but do not play a crucial role in naturally occurring ABRD (27). Some others like serotoninine (28) and platelet activating factor (29) seem to play a significant role in the pathogeny of some pneumonia and the blockage of their specific receptors could improve the treatment of ABRD (30, 31).

6.2.3. Peptides antagonists

Peptides like cytokines (interleukines, tumor necrosis factor), opioids, substance P and neurokine A may play a role in the genesis of lung inflammation (32). The usefulness of their inhibition by specific antagonists or antibodies must still be investigated in ABRD (33).

6.2.4. Inhibitors of cytolytic inflammatory products

Oxygen radicals and several proteases released by activated neutrophiles are

known to be responsible for severe cells injuries in the pneumonic lung (34, 35). These damages could be reduced by the use of antagonists like antioxydants (catalase, superoxyde dismutase, glutathion peroxydase, vitamin A, C and E, iron chelators, etc ...) (36).

6.3. Correction of the mechanical disorders

An excess in the contraction of the pulmonary smooth muscles and in the permeability of the pulmonary capillaries and a lack of appropriate airway clearance can induce severe lung dysfunctions with potential dramatic consequences. The correction of these disorders will decrease the work of breathing (and therefore the risk of diaphragmatic fatigue) (37) and improve the gas exchange, helping the patient to come back from (fatal) positif feedback mechanisms to (saiving) negative ones.

6.3.1. Bronchodilators

Beta 2 mimetic and anticholinergic drugs were showed to be highly active in the prompt treatment of ABRD, mainly when these drugs are given in situ, i.e. by aerosol-therapy, and in association (15).

The possible availability of long-acting aerosol preparations could make of this way of administration a method of choice for the treatment of ABRD, because of its high level of efficacy and innocuity and the low level of residues.

Other drugs like calcium channels blokors (38) and sodium cromoglycate (39) are also potent bronchodilators and need to be investigated in ABRD.

6.3.2. Vasodilators

Inhibition of the vasoconstriction can reduced the pulmonary hypertension and the lung capillary filtration responsible for the occurrence of oedema. Substances like aminophylline (40), pentoxiphylline (41) and sodium nitroprusside (42) could act in this way.

On the other hand, diuretics and aerosolised antifoam agents are also usefull in the management of acute pulmonary oedema.

6.3.3. Increase of mucociliar clearance

Several drugs like N-acetylcysteine, mercaptoethane sulfonate, bromhexine, clenbuterol, theophylline, etc ... are supposed to increase the mucoco-ciliar clearance by different pathways and therefore improve the airway permeability (43-45).

However their ability to significantly increase the clearance rate in pneumonic calves has not yet been clearly demonstrated.

7. Conclusions

The control of ABRD is becoming one of the sine qua none conditions of profit for cattle production. This control includes preventive and therapeutic strategies which must be adapted to several individual factors like age, breed, economical value, severity of the disease, etc ...

8. Summary

This paper analyses the physiological, pathophysiological and pharmacological peculiarities of the bovine pulmonary function in order to propose new strategies for improving the treatment of acute respiratory diseases.

9. Résumé

Cet article analyse les particularités physiologiques, pathophysiologiques et pharmacologiques de la fonction pulmonaire des bovins dans le but de proposer des nouvelles stratégies destinées à améliorer l'efficacité du traitement des pathologies respiratoires aiguës.

10. Zusammenfassung

Dieser Beitrag analysiert die physiologischen, pathophysiologischen und

pharmakologischen Besonderheiten in der Lungenfunktion des Rindes mit dem Ziel, neue Strategien für eine verbesserte Therapie von akuten respiratorischen Erkrankungen vorzuschlagen.

11. References

1. Lekeux, P., Hajer, R., Breukink, H.J., Pulmonary function testing in calves: a technical data. *Am. J. Vet. Res.* 45:342-345. 1984.
2. Gustin, P., Lomba, F., Bakima, J., Lekeux, P., Van De Woestijne, K., Partitioning of pulmonary resistance in calves. *J. Appl. Physiol.* 62:1826-1831. 1987.
3. Close, R., Reinhold, P., Lekeux, P., Signification of the phase angle of the monofrequency forced oscillation method for pulmonary function investigation in calves. In Proceedings: 10th Comparative Respiratory Society Meeting, Urbana (USA), P-10. 1991.
4. Altman, P.L., Dittmer, D.S., Respiration and circulation. Federation of American Societies for experimental Biology, Bethesda, Maryland. 56-57. 1971.
5. McLaughlin, R.F., Tyler, W.S., Canada, R.O., A study of the subgross pulmonary anatomy in various mammals. *Am. J. Anat.* 108:149-158. 1961.
6. Ruiz, A.V., Bisgard, G.E., Tyson, I.B., Grover, R.F., Will, J.A., Regional lung function in calves during acute and chronic pulmonary hypertension. *J. Appl. Physiol.* 37:384-391. 1974.
7. Lekeux, P., Hajer, R., Breukink, H.J., Upper airway resistance in healthy Friesian cattle. *Res. Vet. Sci.* 38:77-79. 1985.
8. Bisgard, G.E., Ruiz, A.V., Grover, R.F., Ventilatory control in the Hereford calf. *J. Appl. Physiol.* 35:220-226. 1973.
9. Lekeux, P., Hajer, R., Breukink, H.J., Effect of somatic growth on pulmonary function values in healthy Friesian cattle. *Am. J. Vet. Res.* 45:2003-2007. 1984.
10. Rollin, F., Desmecht, D., Linden, A., Amory, H., Lekeux, P., Assessment of the ventilatory response to CO₂ in two breeds of calves. In Proceedings: 10th Comparative Respiratory Society Meeting, Urbana (USA), P-12. 1991.
11. Desmecht, D., Linden, A., Amory, H., Lekeux, P., Impaired diaphragmatic function in the pneumonic calf. In Proceedings: 10th Comparative Respiratory Society Meeting, Urbana (USA), S-3. 1991.
12. Gustin, P., Dhém, A.R., Lekeux, P., Lomba, F., Landser, F.J., Van De Woestijne, K.P., Cardiopulmonary function values in double-muscled cattle during muscular exercise. *Vet. Res. Com.* 12:407-416. 1988.
13. Lekeux, P., Art, T., Amory, H., Effect of common bovine respiratory diseases on tidal breathing flow-volume loops. *Vet. Res. Com.* 12:463-473. 1988.
14. Meyrick, B.O., Brigham, K.L., Acute effects of *E. coli* endotoxin on the pulmonary microcirculation of anesthetized sheep. *Lab. Invest.* 48:458-470. 1983.
15. Genicot, B., Close, R., Mouligneau, F., Lekeux, P., Clinical and pulmonary function changes induced by aerosoltherapy during bovine acute respiratory distress syndrome. XVIIth World Buiatrics Congress, St Paul (USA), August 1992.
16. Hodes, D.S., Schnitzer, T.J., Kalica, A.R., Camargo, E., Chanock, R.M., Inhibition of respiratory syncytial, parainfluenza 3 and measles viruses by 2 deoxy-D-glucose. *Virology* 63:201-208. 1975.
17. Mohanty, S.B., Rockemann, D.D., Davidson, J.P., Tripathy, R.N., Ingling, A.L., Chemotherapeutic effect of 2-deoxy-D-glucose against respiratory syncytial virus infection in calves. *Am. J. Vet. Res.* 42:336-338. 1981.
18. Knight, V., Gilbert, B.E., Aerosol treatment of respiratory viral disease. *Lung* 168 (suppl):406-413. 1990.
19. Lekeux, P., Art, T., Effect of enrofloxacin therapy in Shipping Fever pneumonia in feedlot cattle. *Vet. Rec.* 123:205-207. 1988.
20. Gustin, P., Lekeux, P., Landser, F.J., Van De Woestijne, K.P., Will, J., Assessment of respiratory diseases and therapeutic intervention by the forced oscillation technique in feedlot cattle. *Res. Vet. Sci.* 49:319-322. 1990.
21. Ose, E.E., Tonkinson, L.V., Single-dose treatment of neonatal calf pneumonia with the new macrolide antibiotic tilmicosin. *Vet. Rec.* 123:367-369. 1988.
22. Giles, C.J., Grimshaw, W.T.R., Shanks, D.J., Smith, D.G., The efficacy of danofloxacin in the therapy of acute bacterial pneumonia in housed beef cattle. In Proceedings: XVth World Buiatrics Congress, Salvador, Bahia (Brasil). 1172-1177. 1990.
23. Espinasse, J., Van Gool, F., Bayle, R., Canguilhem, R., Shelcher, F., Salat, O., Gau, M., Longo, F., Efficacité de la spiramycine chez le veau dans une bronchopneumonie expérimentale à *Pasteurella haemolytica* A1. In Proceedings: XVth World Buiatrics Congress, Salvador, Bahia (Brasil). 466-471. 1990.
24. Selman, I.E.,

- Allan, E.M., Gibbs, H.A., Wiseman, A., Young, W.B., Effect of antiprostaglandin therapy in experimental parainfluenza type 3 pneumonia in weaned, conventional calves. *Vet. Rec.* 4:101-105. 1984. 25. Kubo, K., Kobayashi, T., Effects of OKY-046, a selective thromboxane synthetase inhibitor on endotoxin-induced lung injury in unanesthetized sheep. *Am. Rev. Respir. Dis.* 132:494-499. 1985.
26. Coggeshall, J.W., Christian, B.W., Lefferts, P.L., Serafin, W.E., Blair, I.A., Butterfield, M.J., Snapper, J.R., Effect of inhibition of 5-lipoxygenase metabolism of arachidonic acid on response to endotoxemia in sheep. *J. Appl. Physiol.* 65:1351-1359. 1988. 27. Gustin, P., Dhém, A.R., Lekeux, P., Lomba, F., Landser, F.J., Van De Woestijne, K.P., Investigation of the effects of histamine inhalation on the tracheobronchial tree of calves by the forced oscillation technique. *J. Vet. Pharmacol. Therap.* 11:374-380. 1988.
28. Desmecht, D., Linden, A., Rollin, F., Amory, H., Lekeux, P., Effect of intravenous and aerosol administration of 5-hydroxytryptamine on pulmonary function values in healthy calves. *Am. J. Vet. Res.* 53,(3):315-320. 1992.
29. Smith, L.J., The role of PAF in asthma. *Am. Rev. Respir. Dis.* 143:100-102. 1991. 30. Linden, A., Desmecht, D., Amory, H., Rollin, F., Lekeux, P., Effets du blocage des récepteurs sérotonergiques de type 2 sur les modifications fonctionnelles respiratoires induites par un challenge à la sérotonine chez le bovin. XVIIth World Buiatrics Congress, St Paul (USA), August 1992.
31. Tokuyama, K., Keller, E.G., Purrell, R., The role of PAF in the pulmonary response to inhaled bacterial endotoxin. *Am. Rev. Respir. Dis.* 143:1345-1349. 1991. 32. Kimman, T.G., Terpstra, G.K., Daha, M.R., Westenbrink, F., Pathogenesis of naturally acquired bovine respiratory syncytial virus infection in calves: evidence for the involvement of complement and mast cell mediators. *Am. J. Vet. Res.* 50:694-700. 1989. 33. Desmecht, D., Gustin, P., Lekeux, P., Ansay, M., Le système nerveux peptidergique du poumon : physiologie, physiopathologie et perspectives thérapeutiques. *Ann. Méd. Vét.* 135:15-31. 1991. 34. Travis, J., Oxidants and antioxidants in the lung. *Am. J. Respir. Dis.* 135:773-774. 1987. 35. Schraufstatter, I.U., Revak, S.D., Cochran, C.G., Proteases and oxidants in experimental pulmonary inflammatory injury. *J. Clin. Invest.* 73:1175-1184. 1984. 36. Halliwell, B., Gutteridge, J.M., Iron and free radical reactions: two aspects of antioxidant protection. *Trends Biochem. Sci.* 11:372-375. 1986. 37. Desmecht, D., Linden, A., Amory, H., Lekeux, P., La fatigue du diaphragme : un risque vital au cours des pneumonies ? XVIIth World Buiatrics Congress, St Paul (USA), August 1992. 38. Ahmed, T., D'Brot, J., Wasserman, M., Muccitelli, R., Robinson, M., Tucker, S., Marchette, B., Effect of verapamil on pulmonary and eicosanoid responses to endotoxin in awake sheep. *J. Appl. Physiol.* 64:1700-1708. 1988. 39. Tuchinda, M., Vichyanond, P., Visitsuntorn, N., Habananonda, S., The role of disodium cromoglycate-metered dose aerosol inhaler in the management of asthma in Thai children. *Asian Pac. J. Allergy Immunol.* 8:117-121. 1990. 40. Foy, T., Marrion, J., Brigham, K.L., Harris, T.R., Isoproterenol and aminophylline reduce lung capillary filtration during high permeability. *J. Appl. Physiol.* 58:34-44. 1979. 41. Welsh, C.H., Lien, D., Worthen, G.S., Weil, J.V., Pentoxifylline decreases endotoxin-induced pulmonary neutrophil sequestration and extravascular protein accumulation in the dog. *Am. Rev. Respir. Dis.* 138:1106-1114. 1988. 42. Wright, P., Ishihara, Y., Bernard, R.G., Effects of nitroprusside on lung mechanics and hemodynamics after endotoxemia in awake sheep. *J. Appl. Physiol.* 64:2026-2032. 1988.
43. Jones, C.D.R., Mucociliary clearance from the calf lung. *Can. J. Comp. Med.* 47:265-269. 1983. 44. Davies, C.P., Webster, A.J.F., The effects of a β_2 -agonist (clenbuterol), and anti-bacterial drugs (trimethoprim with sulphadiazine; oxytetracycline) on calf mucociliary clearance. *J. vet. Pharmacol. Therap.* 12:217-224. 1989. 45. Genicot, B., Mouligneau, F., Lekeux, P., Aérosolthérapie : revue des substances thérapeutiques à impacts bénéfiques pour la fonction pulmonaire. *Ann. Méd. Vét.* 136:110-121. 1992.