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Technical study of some major parameters influencing the performances of an aerosol delivery equipment suitable for calves

B Genicot [1]*, M Peckova [2], R Close [1], JK Lindsey [3], P Lambert [3], P Lekeux [1]

[1] *Faculté de Médecine Vétérinaire, Université de Liège, Laboratoire d'Investigation Fonctionnelle, Bât B42, Sart Tilman, B-4000 Liège, Belgium;*
[2] *Department of Biostatistics, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195, USA;*
[3] *Université de Liège, Faculté d'Économie, de Gestion et de Sciences Sociales, Département de Méthodologie Quantitative, Bât B31, Sart Tilman, B-4000 Liège, Belgium*

Summary — Aerosol delivery equipment, suitable for the treatment of bovine respiratory dysfunctions and including 2 parallely positioned jet nebulizers, was studied in depth in order to determine the optimal working conditions in the field. Indeed, some factors might reasonably alter the performance of this equipment. Among these factors, the influences of the parallel position of jet nebulizers (in order to accomodate the breathing requirements of the cattle and achieve a rapid treatment), of the long feed pipe delivering compressed air (in order to keep the animal away from the compressor unit), and finally of the ambient temperature were studied, this equipment being essentially used during the winter season. This equipment could accomodate the breathing needs of cattle weighing up to 225 kg if a pressure of 600 kPa was developed upstream to the nebulizers. The rate of atomization was significantly reduced when working at ambient air temperatures (272.25 K < T < 274.65 K) close to those encountered in winter. This was especially true when pressure upstream to the nebulizers did not exceed 500 kPa. The immersion of the feed pipe for compressed air in hot water led to an increase in the rate of atomization without raising evaporative water losses, and reduced the drop in temperature in the nebulizer solution. Finally, the rate of atomization significantly increased when the face mask including the nebulizers was maintained so that the nebulizers were in a vertical position or at an angle not less than 60° with respect to the ground.

aerosol / inhalation / inhalation device / respiratory therapy / respiratory drug administration

Résumé — Étude technique de certains paramètres susceptibles d'influencer les performances d'un équipement conçu pour l'administration d'aérosols chez le veau. *Cette investigation a porté sur un équipement spécialement conçu pour traiter certaines dysfonctions respiratoires des bovins.*

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* Correspondence and reprints

Constitué de 2 nébuliseurs pneumatiques disposés en parallèle dans un masque facial, cet équipement permettait de couvrir les besoins respiratoires de bovins atteignant 225 kg. Pour ce faire, une pression de 600 kPa a dû être développée en amont des nébuliseurs. Lorsque la température de l'air ambiant (272,25 K < T < 274,65 K) était proche de celles rencontrées en période hivernale, une diminution significative du taux d'atomisation a été observée. Néanmoins, ce taux d'atomisation s'est accru de manière significative lorsque le tuyau d'adduction d'air comprimé a été immergé dans un milieu à haute température. Cette mesure, qui n'a pas provoqué d'accroissement des pertes d'eau par évaporation, a permis, lors du processus d'atomisation proprement dit, de partiellement prévenir la chute de température enregistrée au sein de la solution devant être atomisée. Enfin, lorsque le masque facial était maintenu de façon telle que les nébuliseurs soient verticaux par rapport au sol ou dans un angle non inférieur à 60° par rapport au sol, le taux d'atomisation a également été accru.

aérosols / inhalation / appareil pour l'inhalation / thérapeutique respiratoire / administration de médicaments respiratoires

INTRODUCTION

Inhalation therapy is often used in the management of human airway obstruction. The principles of this therapy, some aerosol generation processes that could be useful in veterinary medicine, the species in which this technique has been used, the advantages of this technique in the treatment of respiratory diseases, and the technical requirements allowing optimal results have all been described previously (Genicot *et al*, 1992a). Different therapeutic drugs, which may be inhaled and which are characterized by useful functional properties in the treatment of respiratory diseases, are mentioned elsewhere (Genicot *et al*, 1992b). Some of these drugs have already been tested in the field. Indeed, in double-muscled calves suffering from the acute respiratory distress syndrome, the pulmonary dysfunction is at least partly due to a severe bronchoconstriction. The inhalation of anticholinergic and sympathomimetic substances has been proved to be highly efficient on both clinical conditions and lung function parameters (Genicot *et al*, 1992c, 1994). In order to conduct such studies, equipment for drug delivery was conceived. This equipment consists of a snugly fitting face mask, including 2 parallely positioned jet nebulizers (Genicot *et al*, 1994) connected to a 4 m feed pipe, and working with highly compressed air. Given that the minute ventilation ($\dot{V}_e$) and the tidal volume (V_t) are considerably higher in cattle than in humans (Stahl, 1967; Lekeux *et al*, 1984; Gustin *et al*, 1988), and that this technique will only be useful and acceptable in veterinary medicine if the inhalation period does not exceed 5 min, the pressure and the airflow developed in this aerosol system must be much higher than those applied for therapeutic purposes in humans. Furthermore, this equipment is, and will be, primarily used during the winter in unheated areas because the maximal frequency of naturally occurring cases of acute respiratory distress syndrome associated with the bovine respiratory syncytial virus is observed during this season (Fedida *et al*, 1988). During this season, a phenomenon of drug crystallization sometimes appears at the top of the nebulizer liquid feed tubes. This is easily prevented by the immersion of the feed pipe for compressed air in a hot water bath. However, the influence of such a precaution on the nebulizer solution temperature and on the evaporative water losses has not been investigated.

Since these conditions and requirements are specifically encountered in bovine medicine, this study aimed to investigate their influence on the rate of atomization, and on the temperature and concentration changes in the solution being atomized.

MATERIALS AND METHODS

Aerosol delivery equipment

This equipment included 2 parallely positioned Neb-U-Mist® 1730 Up-Draft II™ nebulizers (Hudson RCI, Temecula, CA, USA) connected to a snugly fitting face mask described elsewhere (Genicot *et al*, 1994) and driven with compressed ambient filtered air (Leroy Somer Type Airsec 100).

Airflow and pressure measurement

Airflow and pressure were determined by means of a flowmeter (KDG 53-Kobold) and a manometer (Clippard 309-02, Cinti O, USA), respectively. These instruments were placed upstream to the nebulizers (fig 1).

Investigation and data collection procedure

The following procedures were adopted for each test described below. Before each test, jet nebulizers were dried and filled with 5 ml 0.9% NaCl solution. For the whole duration (5 min) of each test, pressure and airflow were recorded every 30 s. At the end of each test, the residual volume was obtained by determining the weight and the density of the residual solution.
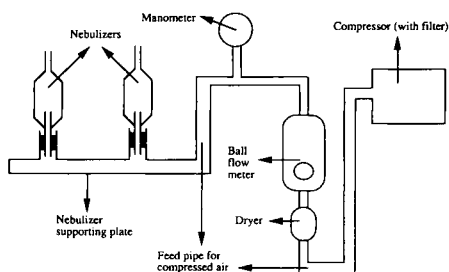

Fig 1. Technical configuration used in this study.

Parameters studied

Air pressure and airflow applied upstream to the nebulizers

These preliminary measurements were performed under laboratory conditions, at ambient temperature ranging from 293.15 to 296.15 K and relative humidity ranging from 40 to 60%. Five pairs of nebulizers were successively tested at 12 different pressures, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600 and 650 kPa. The pressure was enhanced by increasing the air volume admitted to the flowmeter.

Temperature

Low temperature of ambient air to be compressed

In order to investigate the influence of cold compressed air on the airflow and the pressure developed in the delivery equipment and on the rate of atomization, 3 pairs of nebulizers were tested. During this investigation, the compressor and the feed pipe for compressed air were placed in a cold store which was maintained in the temperature range 272.25 to 274.65 K. Airflow, pressure and drug residual volume were recorded as described above. Furthermore, the temperature from cold air trapped in the cold store was recorded every 30 s.

Temperature changes around the feed pipe for compressed air

To investigate the effect of the ambient temperature surrounding the feed pipe (length: 4 m) for compressed air on airflow and drug residual volume, 3 pairs of nebulizers were tested as described above. The feed pipe for compressed air was immersed in a water bath submitted to a slow temperature decrease (311.55 to 274.55 K over 182 min). Pressure, airflow and bath temperature were recorded every 30 s. Drug residual volume was determined as described above.

Furthermore, in order to know whether a change in the temperature of the medium surrounding the feed pipe for compressed air and/or a change in the air pressure applied upstream to the nebulizers exerted a significant influence on the drop in solution temperature and on the evaporative water losses, 36 nebulizers were each

filled with 5 ml 0.9% NaCl solution. As for the other tests, the duration of atomization was 5 min. The sodium level in the initial solution and concentration of solute remaining in the nebulizers were determined using flame spectrometry (Olympus AU 5000, Japan). The temperature change of the solution in the nebulizers was measured using an electronic device described elsewhere (Stockert and Nave, 1974). This temperature was recorded just before the test and every 30 s from the beginning to the end of the atomization process. The temperature of the medium surrounding the feed pipe for compressed air averaged 276.9 ± 0.4 (mean ± SD) and 311.1 ± 0.7 K for nebulizers 1–18 and 19–36, respectively. These different pressures (kPa) were developed upstream to the nebulizers. These pressures were 541 ± 10 kPa (mean ± SD) upstream to nebulizers 1–6 and 19–24, 445 ± 9 kPa upstream to nebulizers 7–12 and 25–30, and 301 ± 9 kPa upstream to nebulizers 13–18 and 31–36.

Position of nebulizers

In order to know whether a change in the position of the 2 parallely positioned nebulizers may influence the rate of atomization, 5 pairs of nebulizers were tested, first in a vertical position with respect to the ground, and then at 80, 70, 60, 50 and 40°. The air pressure in the system was maintained at 500 kPa. Drug residual volume was determined as described above.

Data treatment

Airflow data were corrected (airflow$_c$) for the pressure, the temperature and air density (Houberechts, 1975). The data sets from this investigation were analyzed using the General Linear Models Procedure in SAS®. Logarithmic transformations were decided on the basis of the data plots.

The change of temperature in the nebulizer solution *vs* time was examined using a 1-way analysis of variance. Such an analysis was also used to compare, at each 30-s time-step of the atomization process, the temperatures of nebulizer solution when the temperature of the medium surrounding the feed pipe for compressed air averaged 276.9 ± 0.4 (mean ± SD) and 311.1 ± 0.7 K.

Two-way analyses of variance were used to investigate the effect of pressure and bath temperature on the concentration of solute remaining in the nebulizers at the end of each test, and the effect of the measured pressure and bath temperature on the temperature in the nebulizer solution.

All results are presented as mean ± SD.

RESULTS

Effect of air pressure and airflow applied upstream to the nebulizers

The residual_volume–airflow$_c$ and residual_volume–pressure relationships prevailing under laboratory conditions are displayed in figures 2A and B, respectively. The average total residual_volume was modelled as decreasing linearly with ln (airflow$_c$), which yields the curve for airflow$_c$ in the figure. A similar pattern was obtained with pressure in abscissa.

Residual volume = 12.1190 - 2.4987 ln (Airflow$_c$)
(R-square = 0.916 - P-value < 0.0001)

Residual volume = 16.9150 - 1.9588 ln (Pressure)
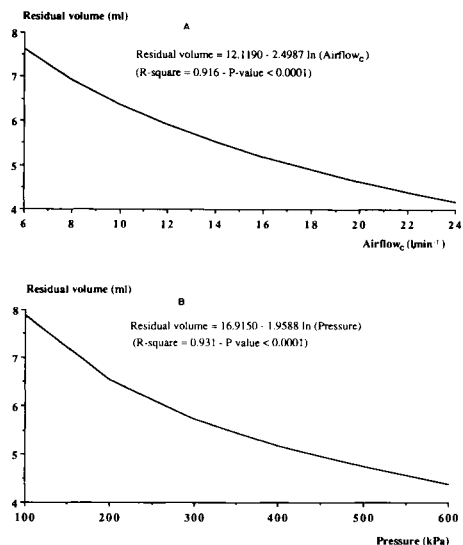(R-square = 0.931 - P value < 0.0001)

Fig 2. Effect of airflow$_c$ (**A**) and pressure (**B**) changes on the residual drug volume. Results under laboratory conditions.

Effect of temperature changes around the feed pipe for compressed air and the low temperature of ambient air to be compressed

The airflow$_c$–pressure, the residual_volume–pressure and the residual_volume–airflow$_c$ relationships were evaluated at ambient air temperatures ranging from 272.25 to 274.65 K and are displayed in figures 3A, B and C, respectively. Within the range 272.25 to 273.15 K, the low temperature of air to be compressed was detected as a factor decreasing the airflow upstream to the nebulizers.

A random effect due to the nebulizers was discovered in the airflow$_c$–pressure relationship for air temperatures ranging from 272.25 to 274.65 K (fig 3A). However, the residual_volume–pressure (fig 3B) and residual_volume–airflow$_c$ (fig 3C) relationships, prevailing under these conditions, did not need a random effect term for nebulizers ($P = 0.1615$ and 0.3015, respectively) and temperatures ($P = 0.8232$ and 0.4345, respectively).

The relationship between the residual volume and the temperature of the bath surrounding the feed pipe for compressed air is illustrated in figure 4 ($P = 0.0046$). The residual volume was enhanced when temperature in the surrounding of the feed pipe for compressed air decreased in the range from 311.55 to 274.55 K. A random effect for pairs of nebulizers was noted ($P = 0.001$). The airflow$_c$ upstream to the nebulizers also exerted a significant effect on the residual volume ($P = 0.0015$).

The concentrations of remaining solute under various nebulization conditions are presented in table I. This concentration was significantly altered by pressure changes developed upstream to the nebulizers ($P = 0.0001$). However, the temperature changes in the medium surrounding the feed pipe for
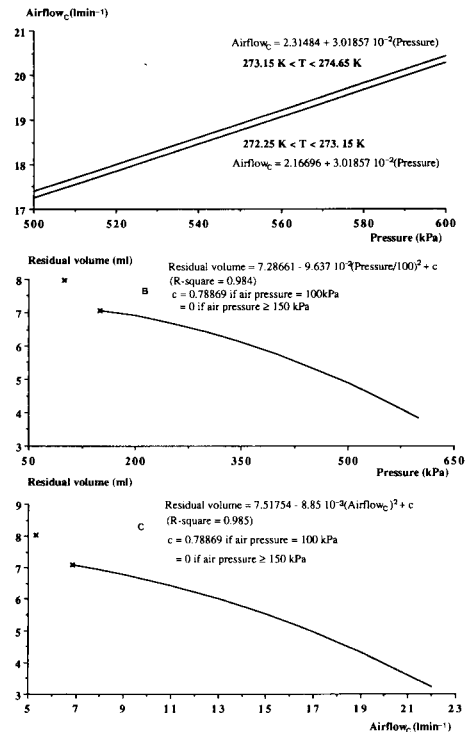

Fig 3. A. Airflow$_c$ (R-square = 0.997, $P < 0.0001$) registered upstream to the nebulizers when the ambient air temperature ranged from 272.25 to 273.15 K and from 273.15 to 274.65 K, the pressure upstream to the nebulizers ranging from 500 to 600 kPa. **B.** Residual volume registered, at different pressures, under ambient air temperature ranging from 272.25 to 274.65 K. **C.** Residual volume registered, at different airflows$_c$, under ambient air temperature ranging from 272.25 to 274.65 K.

compressed air did not significantly modify this concentration ($P = 0,1763$).

The changes in temperature are shown in figures 5 and 6. When the temperature of the medium surrounding the feed pipe for compressed air averaged 276.9 ± 0.4 K, the nebulizer solution temperature fell during the first 150 s (fig 5, $P = 0.001$). On the other hand, when the temperature of the medium surrounding the feed pipe for com-
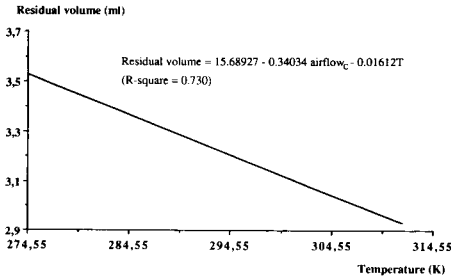
Residual volume (ml)

Residual volume = 15.68927 - 0.34034 airflow$_c$ - 0.01612T
(R-square = 0.730)

Temperature (K)

Fig 4. Residual volume changes observed when the feed pipe for compressed air was submitted to different temperatures. Such a relationship is depicted for an airflow$_c$ of 22.72 l.min^{-1}.

Solution Temperature (K)

A : 276.9 ± 0.4
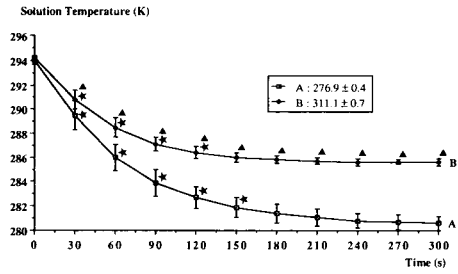B : 311.1 ± 0.7

Time (s)

Fig 5. Changes in temperature of nebulization solution when the feed pipe for compressed air was immersed in a water bath with low (276.9 ± 0.4 K, **A**) or high (311.1 ± 0.7 K, **B**) temperature. ★ Significantly ($P \leq 0.001$) different from values recorded at the prior step; ▲ Significantly ($P \leq 0.01$) different from values recorded when the temperature around the feed pipe for compressed air averaged 276.9 ± 0.4K.

pressed air averaged 311.1 ± 0.7 K, the nebulizer solution temperature fell over a shorter time, *ie* during the first 120 s (fig 5, $P = 0.0001$). Moreover, only 30 s after the start of the atomization procedure, the solution temperature in the nebulizers running with the feed pipe for compressed air averaging 311.1 ± 0.7 K was significantly greater ($P = 0.01$) than that encountered in nebulizers with the feed pipe for compressed air averaging 276.9 ± 0.4 K (fig 5). At every other step of the atomization process, this difference was confirmed ($P = 0.0001$). The higher temperature of the neb-

ulizer solution due to the higher temperature of the feed pipe for compressed air did not modify the final solute concentration (table I).

Under these 2 extreme conditions (276.9 ± 0.4 and 311.1 ± 0.7 K), the pressure changes (fig 6) significantly ($P = 0.0274$) influenced the evolution of nebulizer solution temperature over time.

Table I. Sodium level (mmol/l) in the nebulizer solution before and after the atomization process.*

Nebulizers	Pressure (kPa)	Bath temperature (K)	[Na$^+$] start (mmol/l)	[Na$^+$] end (mmol/l)
1–6	540 (10)	276.4 (0.5)	152.0[a] (0.1)	173.0[b] (1.7)
7–12	450 (10)	276.9 (0.1)	152.0[a] (0.1)	170.3[c] (2.3)
13–18	300 (10)	277.2 (0.2)	152.0[a] (0.1)	168.3[d] (0.6)
19–24	540 (10)	311.0 (0.6)	152.0[a] (0.1)	172.7[b] (0.6)
25–30	440 (10)	311.2 (0.7)	152.0[a] (0.1)	170.3[c] (0.6)
31–36	300 (10)	311.1 (0.9)	152.0[a] (0.1)	166.0[d] (1.0)

[a,b,c,d] Values with different superscripts are significantly ($P < 0.01$) different. * Three pressures were developed upstream to the nebulizers. During the atomization, the feed pipe for compressed air was immersed in a water bath with low (276.9 ± 0.4 K) or high (311.1 ± 0.7 K) temperature. Data are expressed as mean (SD).
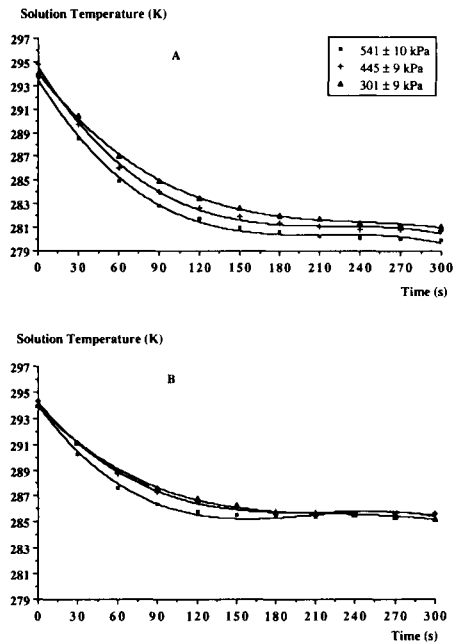
Solution Temperature (K)

Solution Temperature (K)

Fig 6. Influence of the pressure on the temperature changes in the nebulization solution when the feed pipe for compressed air was immersed in a water bath with average temperatures 276.9 ± 0.4 (**A**) and 311 ± 0.7 K (**B**).

Effect of the position of nebulizers

When the nebulizers were vertical to the ground and then lowered to positions ranging from 80 to 40°, an increase (fig 7) in the residual volume was detected.

DISCUSSION

The behavior of jet nebulizers has been investigated previously under conditions prevailing in human medicine (Byron, 1990; Newman, 1991). However, the following include some of the conditions specifically encountered in veterinary medicine: (1) the tandem position of jet nebulizers; (2) the high pressure and airflow values in order to
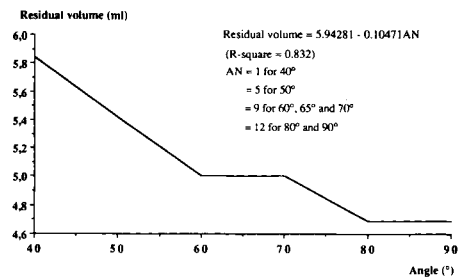
Residual volume (ml)

Fig 7. Residual volume changes observed when nebulizers were vertical to the ground and then lowered to a position ranging from 80° to 40°.

achieve an output volume of drug-carrying air similar to the bovine minute volume; (3) a long feed pipe for compressed air allowing the animal to be kept away from the compressor unit; and (4) working conditions, such as air temperature, near or below 273.15 K. The effects of these conditions have motivated this study.

Data concerning the enhancement of the rate of atomization (fig 2) are in agreement with other studies conducted under conditions prevailing in human medicine (Newman *et al*, 1987). However, the equations (fig 3B and C) predicting the total residual volume under low air temperature (from 272.25 to 274.65 K) are convincingly different from those (fig 2) obtained under laboratory conditions. As can be deduced from the equations reproduced in figures 2B and 3B, when working from 200 to 500 kPa, the configuration which is presently studied atomized lower percentages (table II) of saline water under ambient air temperatures ranging from 272.25 to 274.65 K than under laboratory conditions.

The phenomenon of drug crystallization, which appeared at the top of the liquid feed-tubes of jet nebulizers during clinical trials conducted under winter conditions (Genicot *et al*, 1992c, 1994), was not observed during this technical study. However, due

Table II. Percentages of the initial volume of NaCl solution atomized within the 5 min at various pressures.*

Temperature (K)	Pressure (kPa)				
	200	300	400	500	600
293.15 < T < 296.15	34.6	42.6	48.2	52.6	56.2
272.25 < T < 274.65	31.0	35.8	42.6	51.2	61.8

* The percentages are those encountered under laboratory conditions (ambient air temperature ranging from 293.15 to 296.15 K) and under conditions (ambient air temperature ranging from 272.25 to 274.65 K) close to those encountered during winter (data deduced from equations presented in figures 2B and 3B).

to the energy required for the evaporative water losses, the reduction in nebulizer solution temperature (Cockcroft et al, 1989; Nerbrink et al, 1992; Dahlbäck, 1993) could explain the phenomenon of drug crystallization. A temperature drop of air travelling through the feed pipe for compressed air could also be responsible for such a process. In fact, the results of this study completely support the fact that the enhancement of the temperature around the feed pipe for compressed air enables us to combat the temperature drop of drug solutions within the nebulizers during the atomization process (fig 5) and to raise the atomization rate without increasing the evaporative water losses (table I, fig 4).

The random effects due to the nebulizers can be attributed to a disparity among individual nebulizers. Indeed, design (Nerbrink and Dahlbäck, 1993) and performance (Lux et al, 1993) disparities among individual nebulizers of the same brand have been reported to be caused by manufacturing errors, eg, the air orifice had a different size or shape due to uneven filling in the mould (Nerbrink and Dahlbäck, 1993).

When the pairs of nebulizer were lowered at angles ranging from 90° to 60° with respect to the ground, the residual volume increased by about 3.1% of the initial volume. How-

ever, when lowered from 60° to 40°, this rise was equivalent to 8.4% of the initial volume. This decrease in drug atomization, when the configuration is lowered from 80° to 40°, may be due to the fact that 1 (or 2) of the 3 capillary tubes (nebulizer liquid feed tubes), which are typically situated at 120° intervals around the Neb-U-Mist® 1730 Up-Draft IITM nebulizer feed pipe for compressed air, may become empty before the end of the atomization time (5 min).

Knowing the pressure and therefore the airflow upstream to the nebulizers (fig 3A), the output airflow (l min⁻¹) of the 2 nebulizers can be expressed as a percentage of the minute volume of bovine weighing 150, 225 and 300 kg on average (table III). The allometric equation [1] relating the bovine minute ventilation to the body weight may be used (Gustin et al, 1988).

$$\dot{V}_e = 0.48\ BW^{0.86} \qquad [1]$$

where $\dot{V}_e$ is the minute ventilation (l min⁻¹) and BW is the body weight (kg). In cattle (Lekeux et al, 1984),

$$t_i/t_{tot} = 0.46\ \text{on average} \qquad [2]$$

where t_i is the inspiratory time (s) and t_{tot} is the total time of the breathing cycle (s). Consequently, since

Table III. Output airflow (l min⁻¹) of the 2 nebulizers at different pressures.

Weight ($\overset{\bullet}{V_e}$ l.min⁻¹)	Pressure (kPa)				
	200	300	400	500	600
150 kg (35.70)	46.2	94.3	159.1	240.7	338.9
225 kg (50.60)	32.6	66.6	112.3	169.8	239.1
300 kg (64.80)	25.4	52.0	87.7	132.6	186.7

* This airflow is expressed as a % of the minute ventilation ($\overset{\bullet}{V}e$) of cattle weighing 150, 225 and 300 kg on average.

$$\overset{\bullet}{V_e} = V_i \bullet RR, \qquad [3]$$

where V_i is the inspiratory volume (l) and RR is the respiratory rate (min⁻¹)

$$\overset{\bullet}{V_{ir}} = 1/0.46 \, (\overset{\bullet}{V_e}) \qquad [4]$$

where $\overset{\bullet}{V_{ir}}$ is the real inspiratory airflow (l min⁻¹).

Hence, the ratio of nebulizer output airflow to bovine $\overset{\bullet}{V_e}$ should be at least 2.173. When working at the highest pressure, this equipment for delivering drugs will therefore be able to accomodate the breathing needs of bovine weighing up to 225 kg.

In conclusion, this equipment can completely accomodate the breathing needs of bovine weighing up to 225 kg if a pressure of 600 kPa is developed upstream to the nebulizers. The rate of atomization is significantly reduced when working at ambient air temperatures (272.25 < T < 274.65 K) near those encountered in winter. This is especially true when pressure upstream to the nebulizers does not reach 500 kPa. The enhancement of the temperature around the feed pipe for compressed air combats the temperature drop in the nebulizer solution and raises the rate of atomization without any increase of the evaporative water losses. Finally, the rate of atomization is significantly increased when the face mask including the nebulizers is maintained so that the nebulizers are in a vertical position or at an angle not less than 60° with respect to the ground.

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