DISCUSSION

Since the end of the 1990s, many drugs such as rhDNase, amiloride, new dosages of beta 2-mimetics, prostacyclin analogs, insulin, potential vectors for the gene therapy have been consistently available via the nebulization route. Further, efficacy of nebulizer systems has been improved simultaneously[194]. A large number of diseases including cystic fibrosis, bronchiolitis, COPD, asthma[195-198] but also diabetes, pulmonary hypertension,…[199-202] and of diagnostic tests such as bronchial provocation testing and pulmonary ventilation/perfusion scintigraphy are concerned with nebulizations. This route of administration has many advantages over other routes (oral, intravenous perfusion) such as reduced systemic adverse effects and a quicker onset of action[4].

A large number of parameters may contribute to complicate evaluation of nebulizers. Previous studies have repeatedly shown the great variability in performance of different devices as illustrated in Figure 36.

This variability is well documented and involves unit-to-unit as well as model-to-model aerosol devices[19,20,203,204]. The performance range of nebulizers is quite wide and the choice of underlying physical properties depends on the aims of the nebulization. Indeed, a device adapted to a particular situation could not fit well to another situation. In a comparative study, Faurisson *et al.* highlighted these variations and stated early in 1996, the need of an accurate evaluation of nebulizer performances in order to prescribe the best association between drug and device in clinical practice[167].

If the recent European Standard (EN-FR 13544-1)[1] aims to solve this problem, recent surveys permitting to confirm a gain in quality are still missing. Such variations between devices are likely to dramatically affect the lung dose of drug, particularly in pediatric patients and in those suffering from obstructive lung diseases[205].

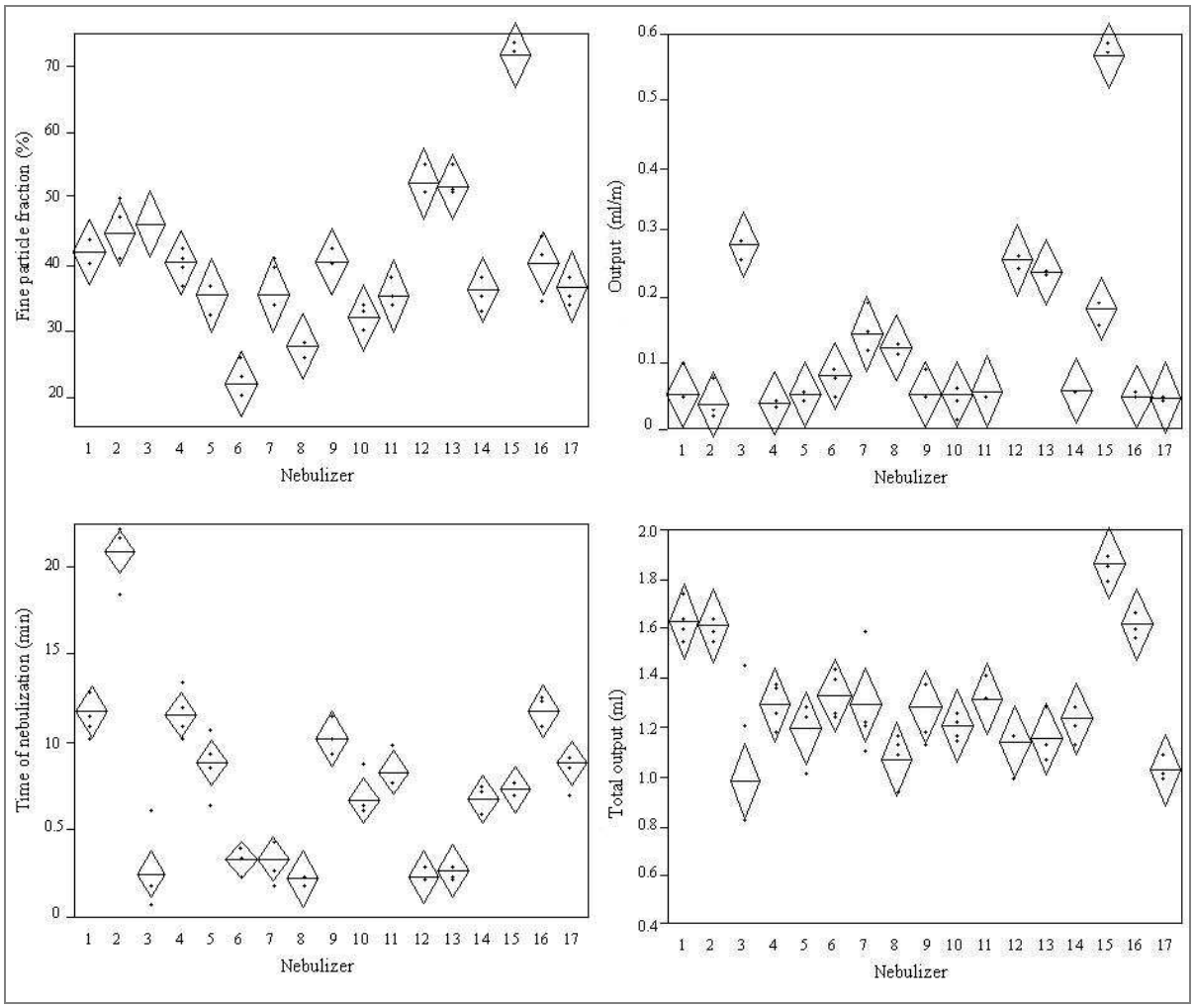


Figure 36 : Variability in fine particle fraction, output, time of nebulization and total output between different nebulizers[19]

The definitions and the expression of different doses (emitted, inhaled or lung dose in percentage of different doses) are occasionally obscure and may contribute to misunderstandings of experimental observations. Assessing particle deposition in the lung is rather a complex issue, since it depends on multiple factors such as particle size distribution produced by the devices used and respiratory conditions of the patient (pattern of breathing, lung disease, position). The situation could be much more complex for diseased lungs since the lung anatomy, the airflow profile, and the ventilation distribution may be altered.

In 2001, the European Respiratory Society (ERS) commissioned a Task Force to review scientific and clinical principles of nebulized therapy and to edit a set of guidelines (evidence-based whenever possible) for users of nebulized treatment in Europe[2]. The technical aspects were evidently detailed and extensively reported in a

review article[206]. It is not astonishing that these guidelines state that we must consider the matching of « the nebulized drug delivery to the performance of nebulizer systems » and recognize that it is therefore difficult to choose the ideal nebulizer for a given application. This choice varies according to the needs of different patient groups or stages of the disease. These guidelines classify nebulizers into three categories according to the particle size provided[207]:

- Nose and throat (ENT) deposition for particles > 5 μm
- Tracheal and bronchial deposition for particles between 2–6 μm
- Deep lung deposition for particles between 0.5–3 μm

Monitoring protocols and evaluation of nebulizers are well established and the aim is the answering of some precise questions:

- What are the aerodynamic properties of emitted particles?
- What is the drug output of the nebulizer?
- How and where the particles deposit into the lungs?

Firstly, it is necessary to perform these protocols in healthy subjects and once the results are obtained, investigations can be done on patients to obtain specific clinical information about nebulization.

Concerning the maintenance of nebulizers, the ERS reminds that nebulizer chambers, tubing and masks should not be re-used for multiple patients unless they have been sterilized (and are capable of withstanding sterilization)[2]. The necessity of a regular cleaning to maintain the initial performances of the nebulizer has been previously demonstrated[154,208,209]. This has been evidences in many studies by the demonstration of bacterial contamination of the material of nebulization in various conditions at home or in the hospital (intensive care-unit[210,211], burn-unit[212], asthmatic patients[213,214], cystic fibrosis patients[215-220]).

CONCLUSIONS AND PERSPECTIVES

Falling under the European guidelines, the aims of our work was to evaluate its nebulization function in healthy subjects but not to evaluate clinically the influence of intrapulmonary percussive ventilation in terms of nebulization efficacy.

In vitro results obtained with cascade impaction or laser diffraction suggest intrapulmonary percussive ventilation produce particles with aerodynamic properties poorly favourable to lung deposition. Moreover, the measurement of drug output let foresee the same evidence. Comparison of lung deposition by tomoscintigraphy and urinary monitoring of nebulized amikacin corroborated these findings. Nebulization combined with IPV resulted in a lower lung deposition and a lower lung dose of drug. The whole body deposition was higher due to a higher extrapulmonary deposition. The distribution of aerosol with IPV was heterogeneous in our group of naive healthy subjects.

The performance of a nebulizer depends on what it is intended to do, on the drug prescribed, on the patient and disease being treated and, on availability and cost in each country[221]. Considering our results, conclusions can be drawn based on proposed guidelines of ERS.

Sidestream and IPV are devices *a priori* well suited for nebulization of drugs since they produce particles adapted to the lung deposition although IPV seems to deliver particles at the lower limit of this range of diameter. Matching the *in vitro* data of aerodynamic properties to the radiolabelled and pharmacokinetic results of deposition must be considered with cautious. The higher cost of IPV and its great variability in lung deposition are major disadvantages. The difficulty of cleaning and disinfection of IPV are also to be taken into account. A large majority of patients included in the studies demonstrating the potential risk of contamination of nebulizers are the same who used intrapulmonary percussive ventilation as physiotherapy. Unfortunately, considering the cost of a patient-circuit of the IPV (about 1000 €), a single disposable use is difficult to apply. Then, disinfection or ideally sterilization must be absolutely realized between patients.

All these results and considerations are clearly unfavourable to IPV and may indicate that IPV is not the first line of choice for drug nebulization. However, if IPV nebulizer function is rather poor - which is not its first indication -, it could be interesting to undertake further research to monitor and investigate the clinical effect in patients with lung disease. Adaptations of the device such as introduction of a speed reducer of particles would also deserve to be studied even though the initial IPV indications must be kept in mind and unmodified.

ADDENDA

Results of the in vitro study evaluating the aerodynamic properties of both devices by cascade impaction (See text in Chapter 2 - § B for details)

1. Sidestream with an entraining flow of 28.3 $L.min^{-1}$

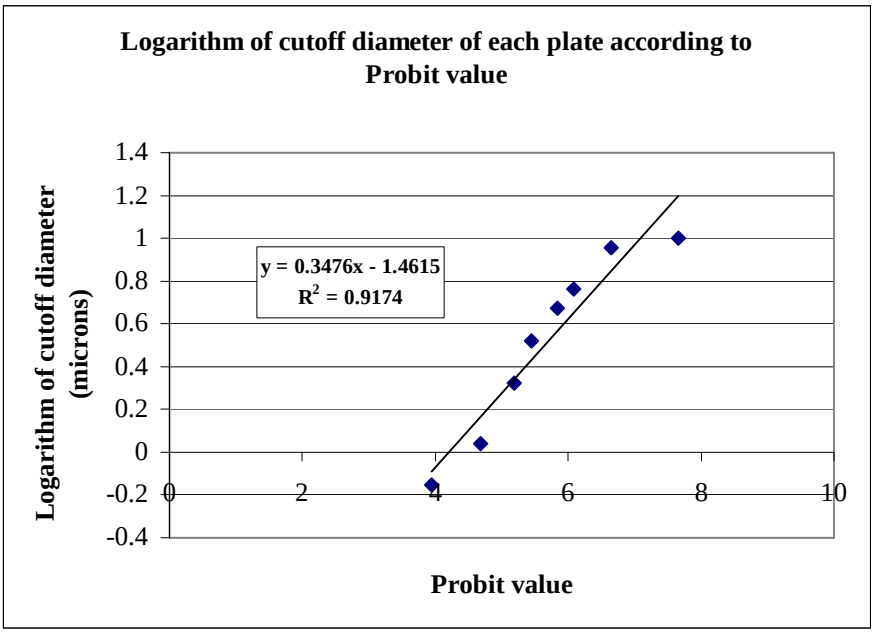
Results of the spectrometry of fluorescence secondary to the cascade impaction and graphical representation of the function y = ax + b where x corresponds to the probit values and y to the logarithms of the cut-off diameter

Blank (N)
3.168
6.506
4.967
Mean
4.880

Stage	Cutoff diameter of plates (microns)	Logarithm of the cut-off diameter of plates	Concentration and mass of Sulforhodamine		Cumulated Mass (ng)	Cumulated mass (% of total mass)	Probit values
			(ng/ml)	(ng)			
Tube			0.539	53.924	13364.2	100.0	
PS			0.000	0.000	13310.3	99.6	
0	10.0	1.000	6.204	620.350	13310.3	99.6	7.652
1	9.0	0.954	11.630	1162.992	12689.9	95.0	6.645
2	5.8	0.763	8.927	892.656	11526.9	86.3	6.089
3	4.7	0.672	16.164	1616.406	10634.3	79.6	5.831
4	3.3	0.519	13.667	1366.744	9017.9	67.5	5.451
5	2.1	0.322	26.423	2642.261	7651.1	57.3	5.181
6	1.1	0.041	30.498	3049.780	5008.9	37.5	4.681
7	0.7	-0.155	19.591	1959.145	1959.1	14.7	3.950
				Sum			
				13364.259			

Probit (5µm)= 6.216	Probit (1µm) = 4.205
% < 5µm = 88.8%	% < 1µm = 21.3%

FPF =	**67.5%**
MMAD =	**1.89 µm**
ED =	**13.4%**



2. Sidestream with an entraining flow of 60 $L.min^{-1}$

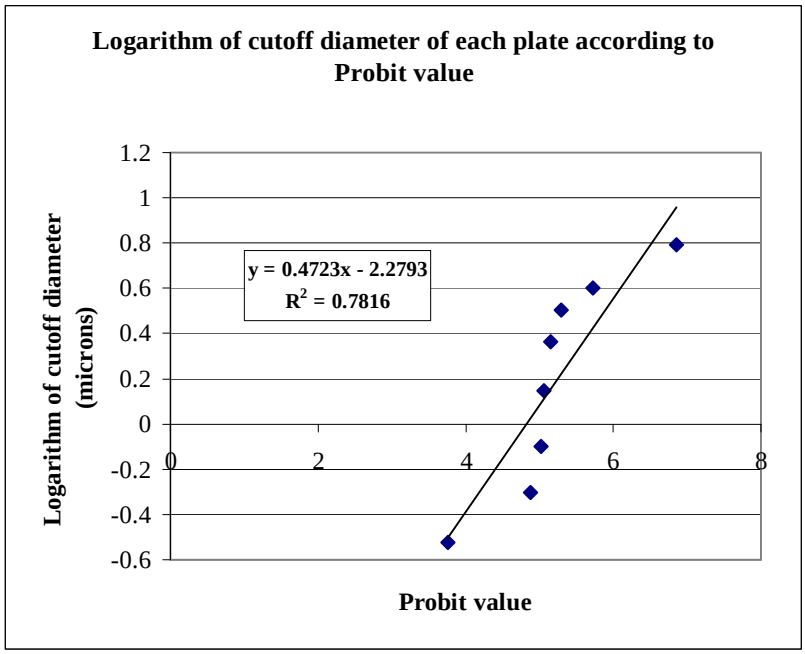
Results of the spectrometry of fluorescence secondary to the cascade impaction and graphical representation of the function y = ax + b where x corresponds to the probit values and y to the logarithms of the cut-off diameter

Blank (N)
3.168
6.506
4.967
Mean
4.880

Stage	**Cutoff diameter of plates (microns)**	**Logarithm of the cut-off diameter of plates**	**Concentration and mass of Sulforhodamine**		**Cumulated Mass (ng)**	**Cumulated mass (% of total mass)**	**Probit values**
			(ng/ml)	**(ng)**			
Tube			3.159	315.859	9967.5	100.0	
PS			0.065	6.533	9651.7	96.8	
0	6.2	0.792	19.992	1999.169	9645.1	96.8	6.852
1	4.0	0.602	15.042	1504.162	7645.9	76.7	5.729
2	3.2	0.505	5.547	554.734	6141.8	61.6	5.295
3	2.3	0.362	3.646	364.568	5587.1	56.1	5.151
4	1.4	0.146	1.245	124.524	5222.5	52.4	5.058
5	0.8	-0.097	5.811	581.109	5097.9	51.1	5.025
6	0.5	-0.301	34.380	3437.980	4516.9	45.3	4.879
7	0.3	-0.523	10.789	1078.898	1078.9	10.8	3.763
				Sum			
				9967.536			

Probit (5µm) = 6.306	Probit (1µm) = 4.826
% < 5µm = 90.4%	% < 1µm = 43.1%

FPF =	**47.3%**
MMAD =	**1.21 µm**
ED =	**9.9%**



3. IPV with an entraining flow of 28.3 $L.min^{-1}$

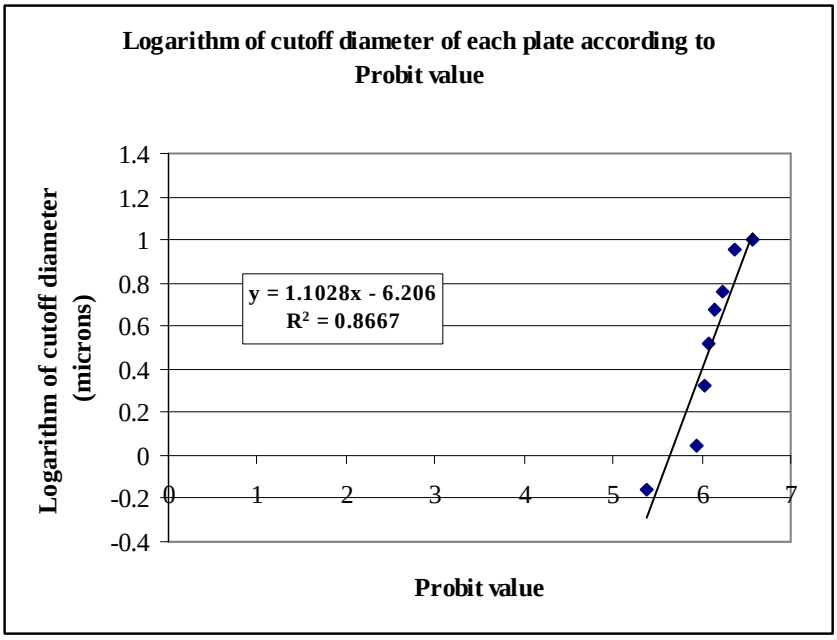
Results of the spectrometry of fluorescence secondary to the cascade impaction and graphical representation of the function y = ax + b where x corresponds to the probit values and y to the logarithms of the cut-off diameter

Blank (N)
3.168
6.506
4.967
Mean
4.880

Stage	Cutoff diameter of plates (microns)	Logarithm of the cut-off diameter of plates	Concentration and mass of Sulforhodamine (ng/ml)	(ng)	Cumulated Mass (ng)	Cumulated mass (% of total mass)	Probit values
Tube			0.745	74.471	1451.8	100.0	
PS			0.109	10.908	1377.4	94.9	
0	10.0	1.000	0.376	37.615	1366.5	94.1	6.563
1	9.0	0.954	0.331	33.103	1328.9	91.5	6.372
2	5.8	0.763	0.254	25.424	1295.8	89.2	6.237
3	4.7	0.672	0.200	20.050	1270.3	87.5	6.150
4	3.3	0.519	0.158	15.826	1250.3	86.1	6.085
5	2.1	0.322	0.343	34.267	1234.5	85.0	6.036
6	1.1	0.041	2.645	264.525	1200.2	82.7	5.942
7	0.7	-0.155	9.357	935.659	935.7	64.4	5.369
				Sum			
				1451.849			

Probit (5µm)= 6.262	Probit (1µm) = 5.628
% < 5µm = 89.7%	% < 1µm = 73.5%

FPF =	**16.2%**
MMAD =	**0.2 µm**
ED =	**1.5%**



Additional results of the in vivo study evaluating lung deposition obtained with both devices by scintigraphy (See text in Chapter 3 – Discussion)

Radioactivity measured by scintigraphy and expressed in percent of the initial radioactivity placed into the collector of Sidestream and IPV

	Residual dose in the collector (% Initial dose)		Dead space of the device (% Initial dose)		Whole Body Deposition (% Initial dose)		Intrapulmonary Deposition (% Initial dose)	
	Sidestream	*IPV*	*Sidestream*	*IPV*	*Sidestream*	*IPV*	*Sidestream*	*IPV*
Mean	65.16	47.31	25.53	37.06	9.31	15.63	4.20	2.49
SD	1.68	2.70	1.56	4.33	1.57	4.24	1.20	2.59
p value	<0.001		<0.001		<0.01		NS	

Publications

Reychler G, Keyeux A, Cremers C, Veriter C, Rodenstein DO, Liistro G.
Comparison of lung deposition in two types of nebulization: intrapulmonary percussive ventilation vs jet nebulization.
Chest. 2004 Feb;125(2):502-8

Gregory Reychler, Caroline Cremers, Cynthia Bosquillon, Rita Vanbever, Jean Roeseler, Pierre Delguste, Giuseppe Liistro
Etude in vitro de deux modes de nébulisation : ventilation à percussions intrapulmonaires vs. nébulisation pneumatique
Kinésithérapie - Mars 2005;Vol 5(38-39):38-41

Reychler G., Wallemacq P., Rodenstein DO., Cumps J., Leal T., Liistro G.
Comparison of lung deposition of amikacin by intrapulmonary percussive ventilation and jet nebulization by urinary monitoring
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LIST OF FIGURES

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