A critical evaluation of the Mefar^{TM} dosimeter

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A critical evaluation of the Mefar^{TM} dosimeter. R.J. Ward, P. Liakakos, R.F. Leonard, D.W. Reid, D.P. Johns, E.H. Walters. ©ERS Journals Ltd 1999.
ABSTRACT: Multicentre studies of airway responsiveness (AR) are increasingly important tools in asthma epidemiology. Because comparisons of AR are made between centres it is essential that measurement techniques are accurate and standard.

This study investigated the Mefar^{TM} dosimeter which is currently used in the 35 centre European Community Respiratory Health Survey (ECRHS) with the next phase currently being planned.

Significant differences were found in driving pressures and aerosol outputs between the three Mefar dosimeters in the laboratory. A linear relationship was also found between driving pressure and aerosol output (R^2=0.96). These differences are important as they may lead to variations between centres of ≤35% in the drug dose delivered in AR measurement, which could potentially diminish the power of individual study centres to accurately detect national differences in AR.

Dosimeter driving pressure and nebulizer output should be standardized in future studies of airway responsiveness. With relatively simple quality control measures in place it is believed that the Mefar dosimeter can produce reliable between-centre longitudinal data with an increase in the accuracy of these important studies.
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Airway responsiveness (AR) is widely used as an objective measure of asthma prevalence [1–3]. AR is increasingly measured by challenge testing with nebulized bronchoconstrictor agents, such as methacholine chloride, using dosimeter systems to gain accuracy [4]. AR is expressed conventionally as provocative dose causing a 20% fall in forced expiratory volume in one second (PD20).

Recent suggestions that asthma prevalence is increasing worldwide [1, 2, 5, 6] have led to the development of major multicentre studies of AR, which may provide a means of establishing risk factors for the development of asthma. The European Community Respiratory Health Survey (ECRHS) was established in 1992 as a cross sectional study [7], but plans are now well advanced in many centres for a second phase follow-up longitudinal study and in some centres for a repeat cross-sectional prevalence study. In such studies, the standardization of measurement methodology is essential as variation in technique between centres, or within centres over time, may directly affect PD20 and therefore interpretation of differences and changes in asthma prevalence.

Dosimeter systems are designed to administer a known quantity of provocative aerosol to determine AR. These systems consist of an electromechanical device which delivers air under pressure to a nebulizer for a specified activation time. There are many dosimeters available but the authors examined the Mefar^{TM} system (Mefar, Brescia, Italy) because of its widespread use and, specifically, because of its uniform adoption in the ECRHS.

The authors have previously raised concerns regarding the operation of the Mefar dosimeter system [8, 9] and as a consequence of this decided to study it in detail and to assess suitability for continued use in the longitudinal and cross-sectional ECRHS studies of AR. The relationships of weight output and true aerosol output to driving pressure and activation time have been examined. Accurate calibration of the Mefar system has been found to be essential to ensure accurate aerosol delivery. It is believed that this information is highly relevant to the ECRHS and that it must be considered if differences in measured AR are to be reliably attributed to differences in asthma prevalence.

Materials and methods

Three Mefar (IV) dosimeters (Mefar) and a set of five new Mefar (Mefar) nebulizers were studied.

Static driving pressure

Static driving pressure was measured without a nebulizer attached to the dosimeter since individual nebulizers have a distinct but variable resistance to flow; and if attached would reduce the down stream measured driving pressure.

Driving pressure was measured with a pressure gauge (Dobbie Instruments, Sydney, Australia) and by a rapid response pressure transducer (Biomedical Engineering, Alfred Hospital, Melbourne, Australia) connected to the dosimeter. The voltage produced from the transducer was digitized and interpreted using data acquisition software

(AqKnowledge; Biopack Systems Inc., Goleta, CA, USA). The pressure transducer was calibrated at five pressures (0, 100, 120, 140, 200 kPa) using medical grade compressed air.

During pressure measurement the dosimeter was programmed with a 6 s delay between activations to allow sufficient pressure to build up in the dosimeter. The output tubing of the dosimeter was connected directly to the pressure transducer. The dosimeters were activated sequentially 10 times, and the peak driving pressure recorded.

Nebulizer output

Nebulizer output was measured gravimetrically on an analytical balance (sensitivity ±0.0001 g) and by an aerosol tracer method using lithium chloride (LiCl) [10]. Briefly, the nebulizer was filled with 4 mL of LiCl solution and activated five times with a 6 s pause between activations. The generated aerosol was entrained onto a glass fibre filter paper and the LiCl subsequently desorbed in 5 mL of double osmosis purified water and the concentration of the resultant LiCl solution measured by flame photometry [10]. The LiCl concentration is taken to represent the aerosol output fraction of nebulized drug [10]. In addition the percentage aerosol output was calculated (*i.e.* per cent of weight loss that represents true drug-containing aerosol output rather than evaporative water loss).

Five nebulizers were calibrated using a dosimeter with an initial driving pressure of 180 kPa. Driving pressures were measured in triplicate before and after the calibrations. One nebulizer was studied with a dosimeter set sequentially at different driving pressures which were achieved by adjusting the pressure control valve inside the dosimeter. A single nebulizer was used to exclude output variation due to nebulizer differences. Measurements were performed in triplicate at 100, 150, 180 and 200 kPa (driving pressure was checked in triplicate before and after measurements).

Activation time

Activation time is the time that driving gas is passed through the nebulizer. Activation time was subdivided into two components, the time taken to reach 95% of peak pressure and the time spent at, or above, 95% of peak pressure.

Activation time is controlled by the Mefar dosimeter with programmable times in increments of 0.1 s. The outputs from the five nebulizers were studied at two activation times of 1.0 and 1.7 s at a static driving pressure of 180 kPa. The Mefar dosimeter activation time was assessed independently and electronically by data acquisition software (AqKnowledge, Biopack Systems Inc.).

Statistical methods

All statistics were performed using Minitab software (Minitab Inc., PA, USA), release 11.0. Weight loss, aerosol output and percentage aerosol output were all related to driving pressure by linear regression and the square of the correlation coefficient (R^2), was calculated. Differences between dosimeters were examined by one way analysis of variance.

Table 1. – Aerosol output of mefar nebulizers for two activation times (driving pressure 180 kPa)

Neb.	Aerosol output mg	
	1.0 s activation	1.7 s activation
1	6.15±0.38	12.29±0.13
2	5.79±0.25	8.12±0.80
3	6.54±0.25	11.83±0.15
4	6.36±0.64	10.66±0.68
5	5.13±0.29	10.34±0.15
Mean	5.99±0.56	10.65±1.63

Output measured in triplicate. Data are presented as mean±SD of three measurements. Neb.: nebulizer number.

Results

Driving pressure

The observed mean static driving pressures, under baseline operational conditions of the three Mefar dosimeters, were 182, 192 and 207 kPa respectively, which were significantly different from each other (p=0.0001). The official "set" pressures described by the manufacturer's under technical information received with these dosimeters were 183, 183 and 186 kPa, respectively.

The aerosol outputs of each nebulizer are shown in table 1. The relationships between weight loss, aerosol output and driving pressure are presented in table 2 and the relationships of weight, aerosol and percentage aerosol output to driving pressure are shown graphically in figures 1 and 2. There was a significant difference between weight and aerosol output (p=0.0006) but the two were correlated (r=0.95). There was a linear relationship between driving pressure and each index of output: with weight loss R^2=0.88 (p=0.0001), aerosol output R^2=0.96 (p=0.0001) and percentage aerosol R^2=0.90 (p=0.0001).

Table 2. – Weight, aerosol and percentage aerosol output at different driving pressures

Pressure kPa	Weight output mg·s^{-1}	Aerosol output mg·s^{-1}	% Aerosol output
100	5.5	2.5	44.9
100	6.4	2.2	34.6
100	7.9	2.4	30.4
Mean±SD	6.6±1.2	2.4±0.1	36.6
150	NA	5.6	NA
150	9.5	5.5	57.4
150	9.7	5.4	56.1
Mean±SD	9.6±0.1	5.5±0.1	56.7
180	9.7	5.8	59.8
180	NA	6.1	NA
180	10.9	6.5	59.9
Mean±SD	10.3±0.8	6.1±0.4	59.8
200	12.4	8.1	65.2
200	12.0	8.0	67.0
200	10.9	8.1	73.6
Mean±SD	11.8±0.8	8.1±0.0	68.6

Outputs measured in triplicate. Data are presented as individual measurements and means±SD shown. Given that the concentration of the tracer (lithium chloride (LiCl)) used was only 0.24 M (1% weight/volume) a direct comparison of weight and aerosol output can be made assuming that 1 μL LiCl solution=1 mg of solution. NA: not available.
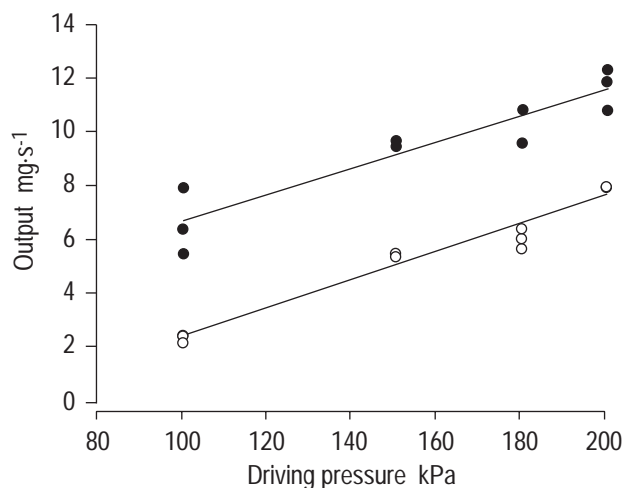
Fig. 1. – Weight and aerosol output at varying driving pressures. All measurements were performed on the same nebulizer with a 1 s activation time under identical conditions. Measurements were carried out in triplicate. ——— : lines of best fit; ●: weight output (R^2=0.88; regression equation: Y=1.66839+5.02E-02X); ○: aerosol output (R^2=0.96; regression equation: Y=2.92606+5.36E-02X).

At a driving pressure of 100 kPa percentage aerosol output was 36% (2.36 ± 0.13 mg·s^{-1}) compared to 62% (6.15 ± 0.38 mg·s^{-1}) at 180 kPa (table 2).

Activation time

Driving pressure plotted against activation time is shown in figures 3a and 3b. Compartmentalization of the timing (*i.e.* time to peak pressure, and time at peak pressure) is presented in table 3. At a programmed activation time of
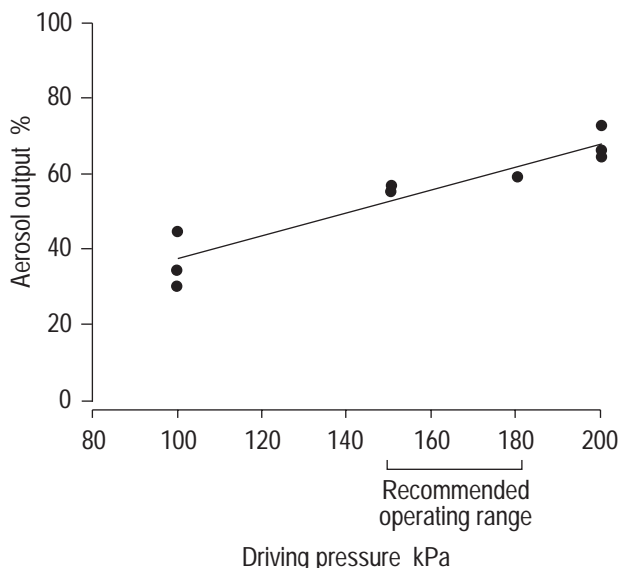

Fig. 2. – Percentage aerosol nebulizer output (AO) at varying driving pressures. Percentage aerosol represents the aerosol fraction of total weight loss, calculated as: %AO=(AO/weight output) × 100. ——— : line of best fit; ●: % AO (R^2=0.90; regression equation: Y=6.12811+0.311984X). The recommended operating range is that supplied by the manufacturer with the dosimeter operating instructions.
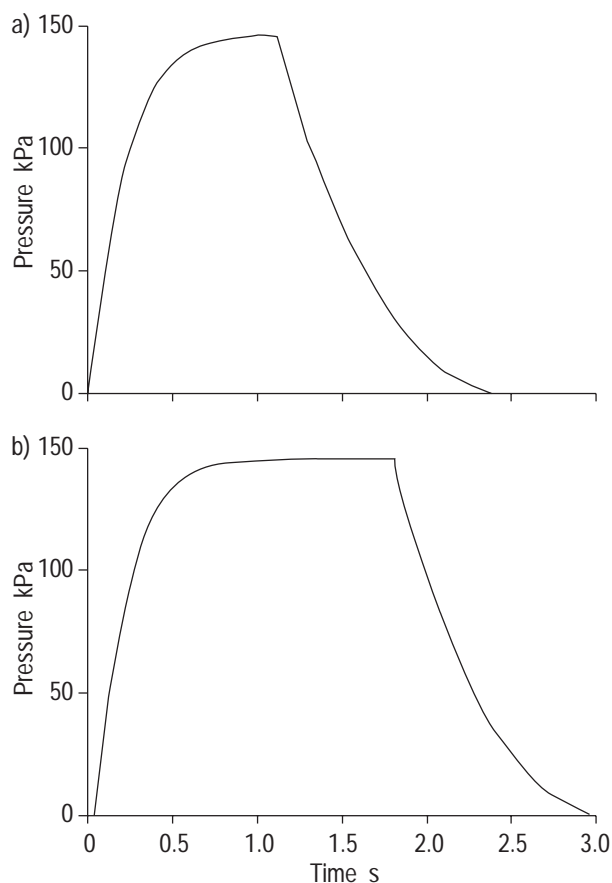

Fig. 3. – Dynamic pressure plotted against time. (Pressure measured from an in line pressure transducer down stream from the test nebulizer). a) 1.0 s activation time. b) 1.7 s activation time.

1 s (and a driving pressure of 180 kPa) 48% (0.5 s) of time was spent at peak pressure. This figure increased to 69% (1.2 s) at a programmed activation time of 1.7 s.

For a 1-s activation time the mean aerosol output was 5.99 mg·s^{-1} at 180 kPa. Using this value the activation time required to produce a mean aerosol output of 10 mg·s^{-1} was calculated to be 1.67 s. The closest programmable time to this with the dosimeter was 1.7 s, calculated to produce a mean aerosol output of 10.19 mg. The actual mean measured aerosol output at this adjusted activation time was 10.60 mg·s^{-1} (SD 1.63 mg·s^{-1}).

Table 3. – Breakdown of activation time (driving pressure 180 kPa)

	Programmed activation time	
	1.0 s	1.7 s
Peak (dynamic) pressure kPa*	147±0.6	144±0.6
95% Peak pressure kPa	140±0.6	137±0.0
Time to 95% peak pressure s	0.6±0.0	0.6±0.0
Time at 95% peak pressure s	0.5±0.0	1.2±0.1
Total activation time s	1.1±0.0	1.8±0.1
Percentage of activation time spent at 95% of peak pressure	48±0.0	69±1.2

Data are presented as mean±SD of three measurements. *: measured with nebulizer in the circuit therefore observed pressure lower that the up-stream 180 kPa static pressure.

Discussion

Significant differences in output between Mefar nebulizers using the same dosimeter have been reported previously [9–11]. However the marked differences in operational driving pressures between Mefar dosimeters observed in this study were unexpected. The data show that aerosol output is directly proportional to driving pressure, so that the differences in driving pressure seen in this study (182–207 kPa) would result in up to a 31% difference in aerosol output between dosimeters even with the same nebulizer connected. These differences arise solely from driving pressure variation and occur before any effect of nebulizer variation has been taken into account. This finding has important implications for multicentre studies which seek to compare challenge data and may result in artificial differences in AR between centres.

In the manufacturer's instructions which accompany the dosimeter, Mefar recommends that dosimeters should operate between 152 and 182 kPa. Indeed each dosimeter is theoretically "set" with an individual driving pressure marked on the dosimeter. However, observed pressures differed from these "set" pressures. It is possible that the activation pressures may have drifted with sustained use, but, if this is the case, then it should be pointed out that the same trend would almost certainly be reflected in other dosimeters used in the ECRHS.

In clinical terms it can be calculated from the regression of driving pressure against aerosol output (fig. 1) that a PD_{20} of 2 mg obtained from a dosimeter operating at 182 kPa would become 2.6 mg at 152 kPa. This represents a 23% difference in output (and hence PD_{20}) even within the range recommended by Mefar. Two of the dosimeters were working outside this range, and at the extreme observed in this study (207 kPa) the PD_{20} in the same hypothetical individual would become 1.7 mg. This represents a potential 35% difference in PD_{20} that would be measured in an individual between a dosimeter working at 152 and 207 kPa.

For PD_{20}s to be directly comparable, the operating pressure of the Mefar dosimeter should be standardized and checked regularly. The data show that at increased driving pressures the nebulizer performs more efficiently, producing a greater percentage aerosol output. As a consequence a driving pressure of 180 kPa is recommended, since it is still within the recommended limits but represents a satisfactory aerosol output. In addition, there is evidence that higher operating pressures produce more particles within the respirable range <5 μM [12–14].

The results suggest that, the very least, driving pressure always needs to be stated to make sense of data given for Mefar nebulizer output. Thus, in a recent study providing post-study calibration of nebulizers used in the ECRHS, [11] a mean aerosol output of 43% was reported. It was subsequently commented that this output was unexpectedly low for a modern nebulizer system [8]. This performance profile would be consistent with the Mefar dosimeter being set at a low driving pressure. Extrapolation from the present regression data would suggest that the pressure used was 143 kPa, which is outside and below the manufacturer's stated specification of driving pressure.

The same investigators [11] suggested that the use of log dose response (LDR) rather than PD_{20} would limit the effect of differences in nebulizer output between centres providing that the within-centre coefficient of variation is small. They demonstrated a low coefficient of variation between batches of nebulizers but these nebulizers were all calibrated in a single centre presumably using a single dosimeter working at a single uniform pressure. This would not be representative of actual field conditions, where a wide range of dosimeter driving pressures are likely to exist. The experience of the current authors would suggest that significant differences exist between dosimeters even within one centre.

The LDR is a useful index, but it is felt that, wherever possible, PD_{20} should still be the measurement of choice in studies of AR. This is of particular significance in longitudinal studies where the repeatability of the PD_{20} is well characterized but where LDR repeatability has yet to be fully assessed [11]. A recent study suggests that the use of LDR is acceptable only at levels of AR where PD_{20} is actually measurable [15].

The Mefar system is designed to achieve an output of 10 mg of solution per dose. In this study it has been shown that if nebulizer activation time is increased to account for evaporative loss then a true aerosol output of 10 mg can be easily achieved. In the case of the nebulizers used in this study, this was achieved by changing the activation time from 1.0 to 1.7 s.

Increasing the activation time to correct for evaporative loss will impact on the results in epidemiological surveys because, effectively, 40% more drug is being nebulized, thus leading to a greater number of subjects with a measurable PD_{20}. Consequently, there will be less statistically censored PD_{20} data, which would increase the statistical power of studies which seek to use PD_{20} to represent asthma prevalence. This insight also emphasizes why it is important to know the true aerosol output before meaningful comparisons can be drawn from data obtained by different centres. It has previously been pointed out that major confounding, in apparent changes in asthma prevalence, can potentially arise when changes are made in equipment without appreciating the impact on aerosol output [16].

In conclusion, it is recommended that dosimeters be checked on a regular basis to ensure that an adequate driving pressure is being used. This is a relatively simple task using a standard pressure gauge that would be available in any clinical lung function laboratory. Even so, it is also recommended that all nebulizers be calibrated by an aerosol tracer method, such as the lithium chloride method, at a stated driving pressure. Many centres are now making active plans for the next phase of the European Community Respiratory Health Survey and the current findings are therefore extremely timely and pertinent. Relatively minor and technically simple changes to laboratory routines would add greatly to the quality control of airway responsiveness measurements.

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