Comparison of EPAG and Respironics Next Generation Impactor Test Protocols using Cooled and Ambient Conditions

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Summary

A recent EPAG study[1] reported a significant difference in MMAD between a cooled and ambient Next Generation Impactor (NGI) when air was entrained directly in to the impactor without first passing through the nebulizer. Stapleton and Finlay[2] calculated that air is saturated at the exit of a nebulizer mouthpiece. We therefore included a seal between nebulizer and impactor to ensure all air passed through the nebulizer prior to entering the impactor. Results show the inclusion of a seal produces a less significant difference in MMAD between cooled and ambient conditions. We conclude the air exiting the mouthpiece of a nebulizer is substantially saturated under ambient conditions and droplet downsizing in the impactor itself is potentially not as great as reported when air is entrained after the mouthpiece.

Introduction

The downsizing of droplets in impactors is a subject of debate. Droplet downsizing in cascade impactors has been observed. It has been suggested that this is due to the impactor being at much higher temperature than the solution being delivered and thus evaporation takes place in the impactor so to achieve saturation. Stapleton and Finlay demonstrated this with a solution cooled to 10°C and delivered into an ambient impactor[3]. It is proposed by EPAG and reported by Berg et al that refrigeration of the impactor would prevent this evaporation and thus droplet downsizing[4]. However, other reports have suggested that downsizing is not significantly different between ambient and cooled impactors[5].

It is anticipated that the Next Generation Impactor will become the accepted apparatus for determining the mass median aerodynamic diameter of liquid aerosol droplets delivered by nebulizers[1], wherein an operational flow rate of 15L/min will be recommended, in accordance with method guidelines outlined in the CEN standard EN-13544:2007[6] and that cooling the impactor may be recommended.

The EPAG validation study reported by Berg et al noted a significant difference in droplet size between cooled and ambient impactors which they ascribed to a reduction in droplet evaporation in the cooled impactor. In the EPAG validation study no mouthpiece was used and the join between the LC Plus nebulizer (Pari GmbH, Starnberg, Germany) and impactor throat was not sealed, allowing entrainment of unsaturated air into the impactor system after the mouthpiece and creating an environment in which evaporation would take place. In the cooled impactor this evaporation does not take place as the unsaturated room temperature air is saturated at the lower temperature. However, where the nebulizer is connected directly to the NGI, saturation occurs in the mouthpiece[2] before the aerosol enters the NGI so the downsizing in the impactor would be significantly reduced. The measured droplet size in the ambient impactor would therefore be a truer reflection of the droplet size leaving the mouthpiece.

We investigated the influence on MMAD of entraining ambient air into the impactor system, coupled with cooling the impactor for increasing periods of time.

Methods

The Next Generation Impactor was operated as per the EN-13544-1:2007 E guideline at 15 L/min using the HCP5 Copley pump after fixed periods of time cooling in a domestic refrigerator at 2-6°C; 0 minutes (ambient), 15 minutes, 45 minutes and 90 minutes, to cover the same temperature range as tested in the Berg[4] publication.

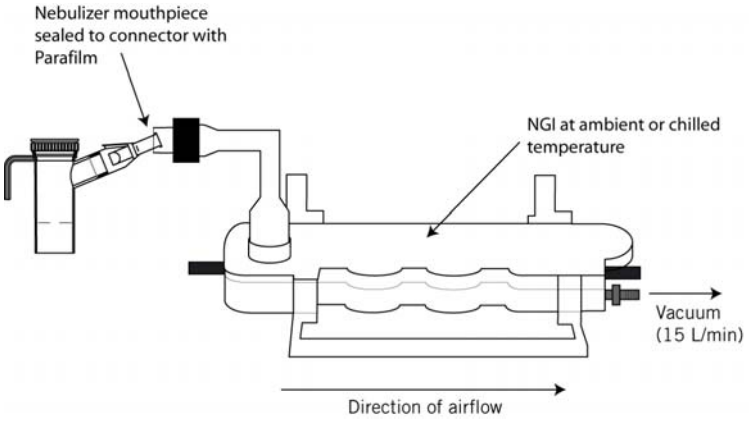
All tests used an LC Plus nebulizer that was filled with 2 mL Salbutamol sulphate [5 mg/2.5 mL IVAX] and operated at 5.5 L/min at 4.0 bar to deliver aerosol for 3 minutes into the impactor circuit.

Two test methods were examined, as follows:

a) Respironics test method:

The LC Plus nebulizer was used with a standard LC Plus nebulizer mouthpiece, and the mouthpiece was sealed with Parafilm to the USP throat of the NGI via a connector.

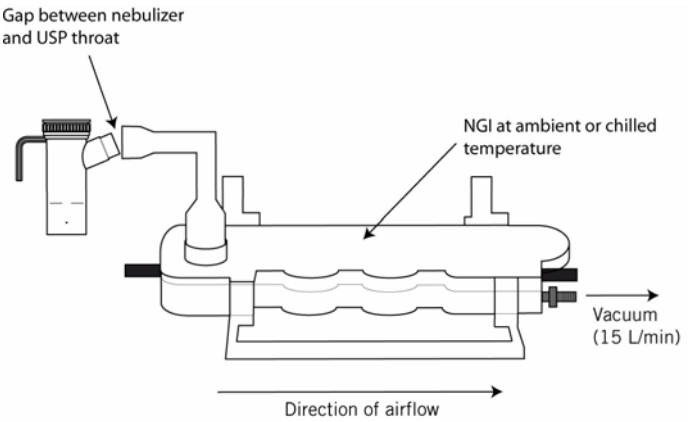
Figure 1: Respironics Test Method Set-up



b) EPAG test method:

No mouthpiece was used and no seal was placed between the LC Plus nebulizer and USP throat. The nebulizer was placed 1cm in front of the USP throat opening.

Figure 2: EPAG Test Method Set-up



Results

Table 1: Mass median aerodynamic diameter and standard deviation of salbutamol aerosol delivered by LC Plus nebulizer into three different test set-ups (n = 3, Berg n = various).

NGI Time in Fridge	MMAD			SD		
	Respironics Method	EPAG Method	Berg JAM 2007 20:2 Data	Respironics Method	EPAG Method	Berg JAM 2007 20:2 Data
0	3.12	2.47	2.07	0.11	0.13	#
15	3.34	2.97	2.72	0.09	0.04	#
30	*	*	2.83	*	*	#
45	3.44	3.39	*	0.10	0.06	*
60	*	*	2.91	*	*	#
90	3.66	3.57	2.97	0.06	0.07	#

* test not carried out

no data available

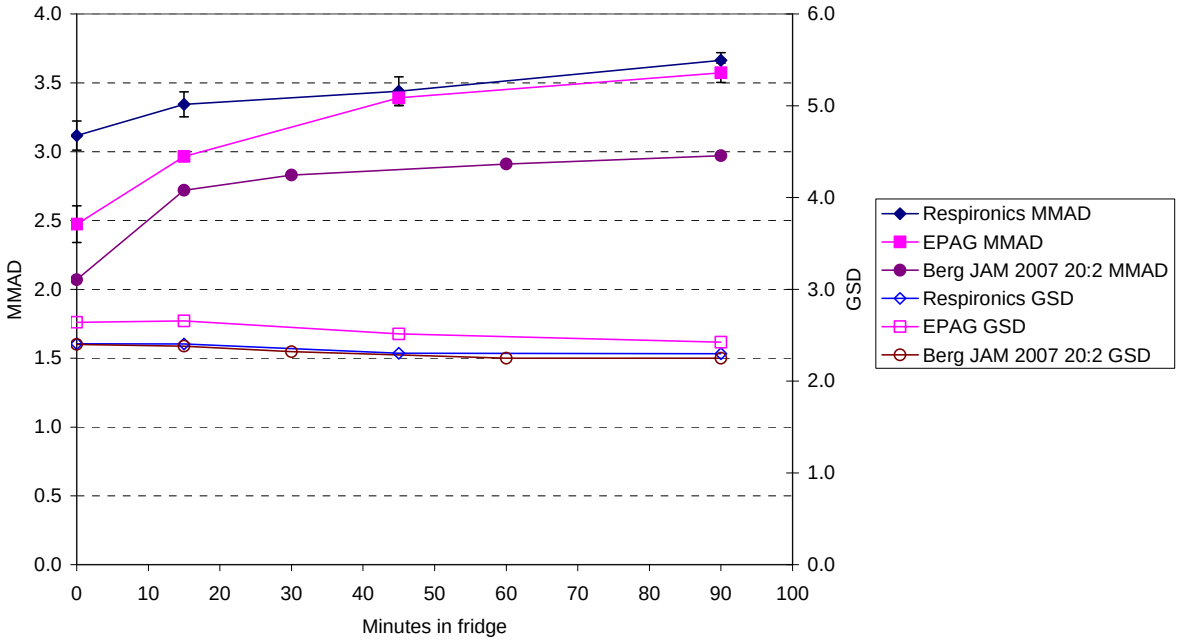
Table 2: Geometric standard deviation and standard deviation of salbutamol aerosol delivered by LC Plus nebulizer into three different test set-ups (n = 3, Berg n = various).

NGI Time in Fridge	GSD			SD		
	Respironics Method	EPAG Method	Berg JAM 2007 20:2 Data	Respironics Method	EPAG Method	Berg JAM 2007 20:2 Data
0	2.41	2.64	2.40	0.02	0.01	#
15	2.40	2.65	2.38	0.04	0.04	#
30	*	*	2.32	*	*	#
45	2.30	2.51	*	0.01	0.02	*
60	*	*	2.25	*	*	#
90	2.30	2.42	2.25	0.00	0.02	#

* test not carried out

no data available

Figure 3: MMAD and GSD of Salbutamol aerosols delivered by the LC Plus nebulizer into NGI refrigerated for various periods of time (n = 3, Berg n = various).



Data from Tables 1 and 2 are represented in Figure 3 and indicate a clear difference in MMAD for ambient NGI conditions between the Respironics method and EPAG method used in the Respironics laboratories. MMAD using the Respironics method is circa 0.8 micron larger than MMAD using the EPAG method in an ambient impactor.

Discussion

The physical difference between these methods is that for the Respironics method, the join between the nebulizer (with mouthpiece) and the induction port was sealed. The EPAG method uses no seal and places the nebulizer in front of the induction port only, therefore allowing additional ambient air (~22°C and ~50% relative humidity) to be entrained into the impactor at its entrance causing droplets to shrink during transit through the impactor as they transfer their mass to their surrounding air in order to achieve equilibrium.

Figure 3 also shows that as the period of NGI cooling increases, MMAD for the Respironics method increases marginally, but MMAD for the EPAG method increases markedly by more than 1 micron and comes into line with that of the Respironics method. The increase in droplet size in the cooled impactor with the EPAG method is due to the 50% relative humidity air introduced at the impactor inlet at 22°C being at equilibrium at 10°C. This increase is not observed when the mouthpiece is sealed to the inlet since the air is saturated at exit of the mouthpiece when it enters either an ambient or cooled impactor. The small MMAD difference in the cooled

impactor compared to ambient impactor could be due to droplet growth at the lower temperature rather than downsizing at the higher since droplets are known to grow hygroscopically in supersaturated environments[7].

When we compared data to the data presented by Berg et al[4], we found that the relative increase in MMAD with increasing cooling time is broadly similar for the two laboratories when the EPAG method is used.

Conclusions

The large degree of downsizing of droplets in an ambient impactor when using the EPAG test setup is a consequence of additional unsaturated air being entrained after the mouthpiece but before the impactor. Even with cooling to compensate for this, the test set-up does not represent the droplet size being delivered to the patient from a nebulizer mouthpiece.

In the Respironics method, there is no introduction of ambient air at the mouthpiece and it can be seen that the MMAD is less subject to change with cooled conditions.

We conclude the air exiting the mouthpiece of a nebulizer is substantially saturated under ambient conditions and droplet downsizing in the impactor itself is potentially not as great as reported when air is entrained after the mouthpiece.

Further investigation needs to be carried out to determine if, when the nebulizer mouthpiece is sealed to the impactor, the small difference in MMAD between ambient and cooled impactors seen here is due to downsizing of droplets in the ambient impactor or due to growth of droplets in the cooled impactor. It would also be pertinent to attempt to clarify which impactor condition is most representative of the true droplet size at the exit of the nebulizer mouthpiece before recommendations on the requirement for appropriate impactor temperatures are confirmed.

References

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